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British Journal of Anaesthesia

OFFICIAL JOURNAL OF
THE ROYAL COLLEGE OF ANAESTHETISTS

Editor: GRAHAM SMITH

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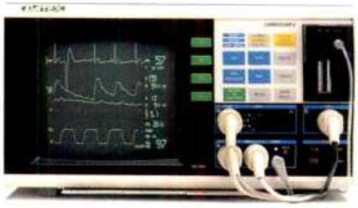

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The purpose of *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the Journal and permission to republish must be obtained from the Editor.

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Three copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), qualifications and full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Each of the three copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the two other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

- Title page
- Summary
- Introduction (not headed)
- Methods
- Results
- Discussion
- Acknowledgements
- List of references
- Tables
- Illustrations

Title page

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succint account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

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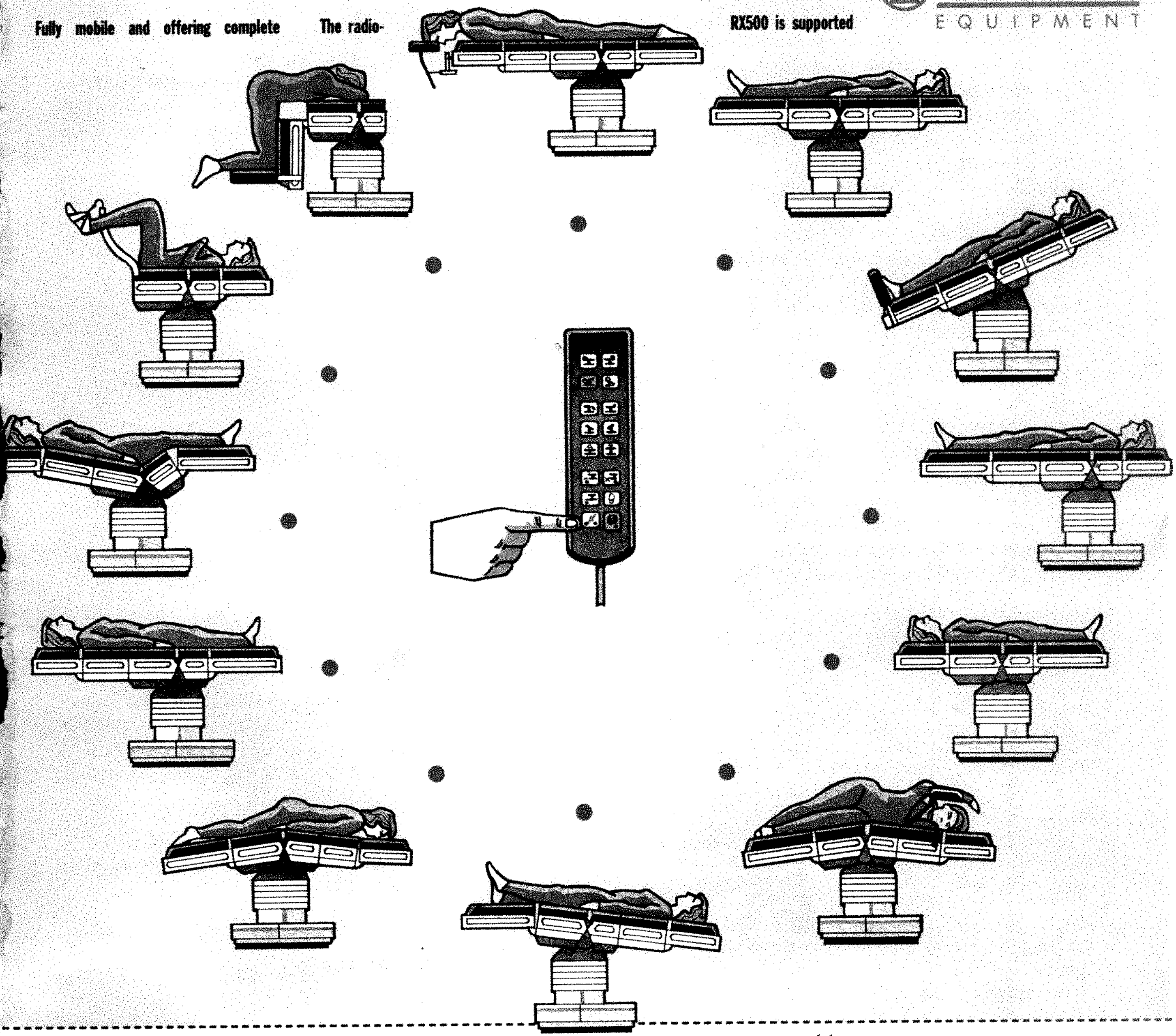

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There should be a table of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legends should be identified by arabic numbers appearing in the text in square brackets.

Use the style of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. The titles of journals must be given in full.

The names and initials of *all* authors should be listed.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted *and accepted* for publication should be included in the list, the phrase "in press" replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

Examples of correct forms of references:

Journals (list *all* authors):

1. Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics. *British Journal of Anaesthesia* 1987; **59**: 14–23.

Chapter in a Book:

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3. Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois: Charles C. Thomas, 1979.

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All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

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C	Blood-Gas Analysis	(l.c. roman)
D	*The Action of Drugs*	(italics, centre)
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F	*Volume.* Large volumes...	(italics, indent)

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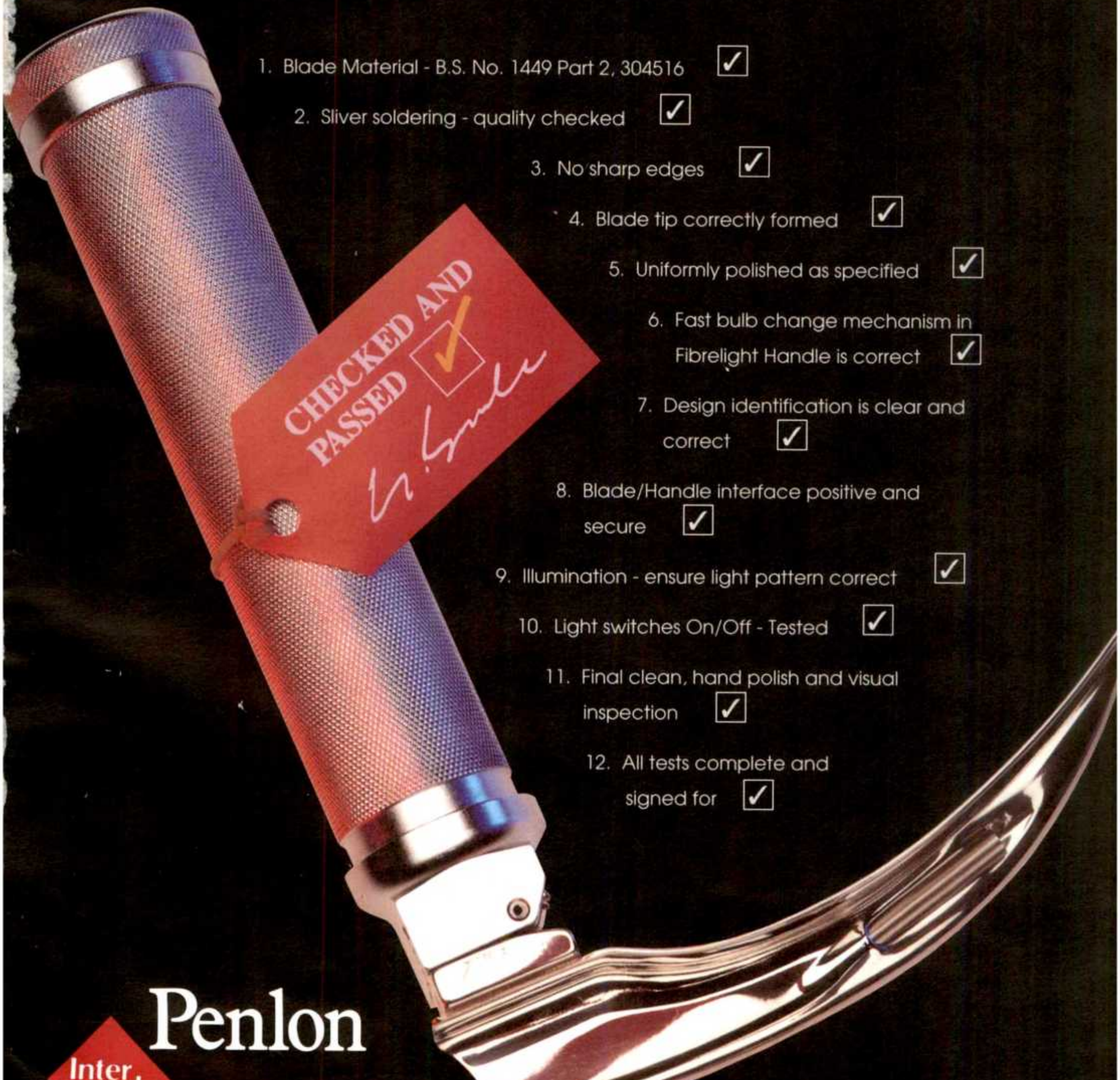

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Format. Summary; Introduction (not headed); Methods and Results; Comment.

Size. Not more than: 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

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These should be corrected and returned to the technical editor *within 48 hours of receipt.* Overseas contributors should return their proofs by air mail.

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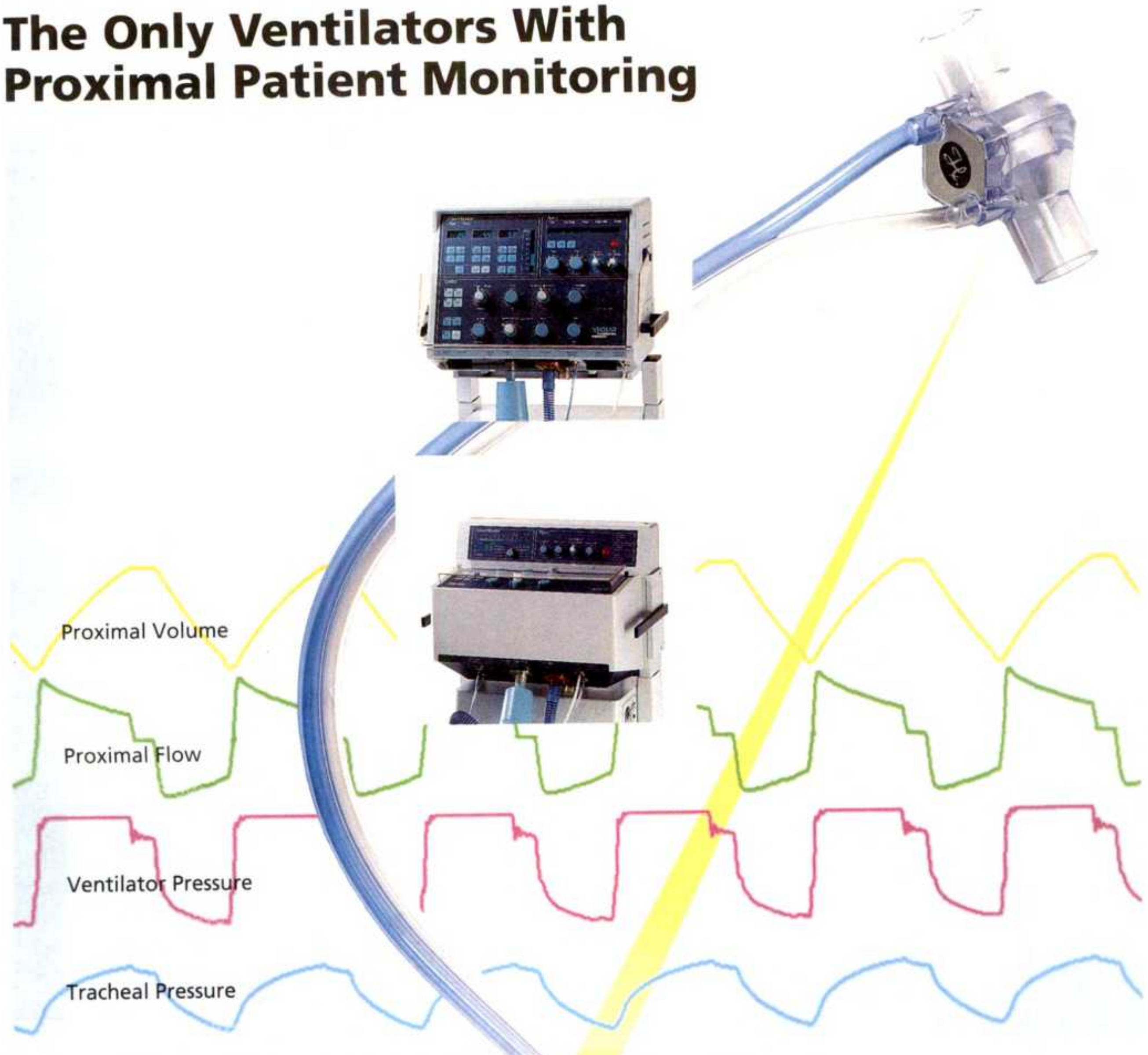

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Speakers will include: Prof. J. G. Jones, Dr C. Wilkins, Dr M. Hamilton-Farrell and Dr P. Janes.

Registration fee £15.

For further information, please contact:
Dr P. N. Reed, Department of Anaesthesia, Peterborough District Hospital, Peterborough PE3 6DA.
Tel: 0733 67451.

WEST OF SCOTLAND COMMITTEE FOR POSTGRADUATE MEDICAL EDUCATION SUB-COMMITTEE IN ANAESTHESIA

THE LAW AND THE ANAESTHETIST

Glasgow October 19, 1992

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A buffet supper will be provided after the meeting, which is sponsored by the Medical and Dental Defence Union of Scotland.

Topics will include:

How to Avoid Litigation	Professor A. R. Aitkenhead, University Department of Anaesthesia, Queen's Medical Centre, Nottingham.
Reporting of Death Under Medical Care	A member of the Glasgow Procurator Fiscal's Office.
Crown Indemnity and Trust Status	Dr I. G. Simpson, Medical and Dental Defence Union of Scotland.

Registration Fee: £5.
Application forms from:
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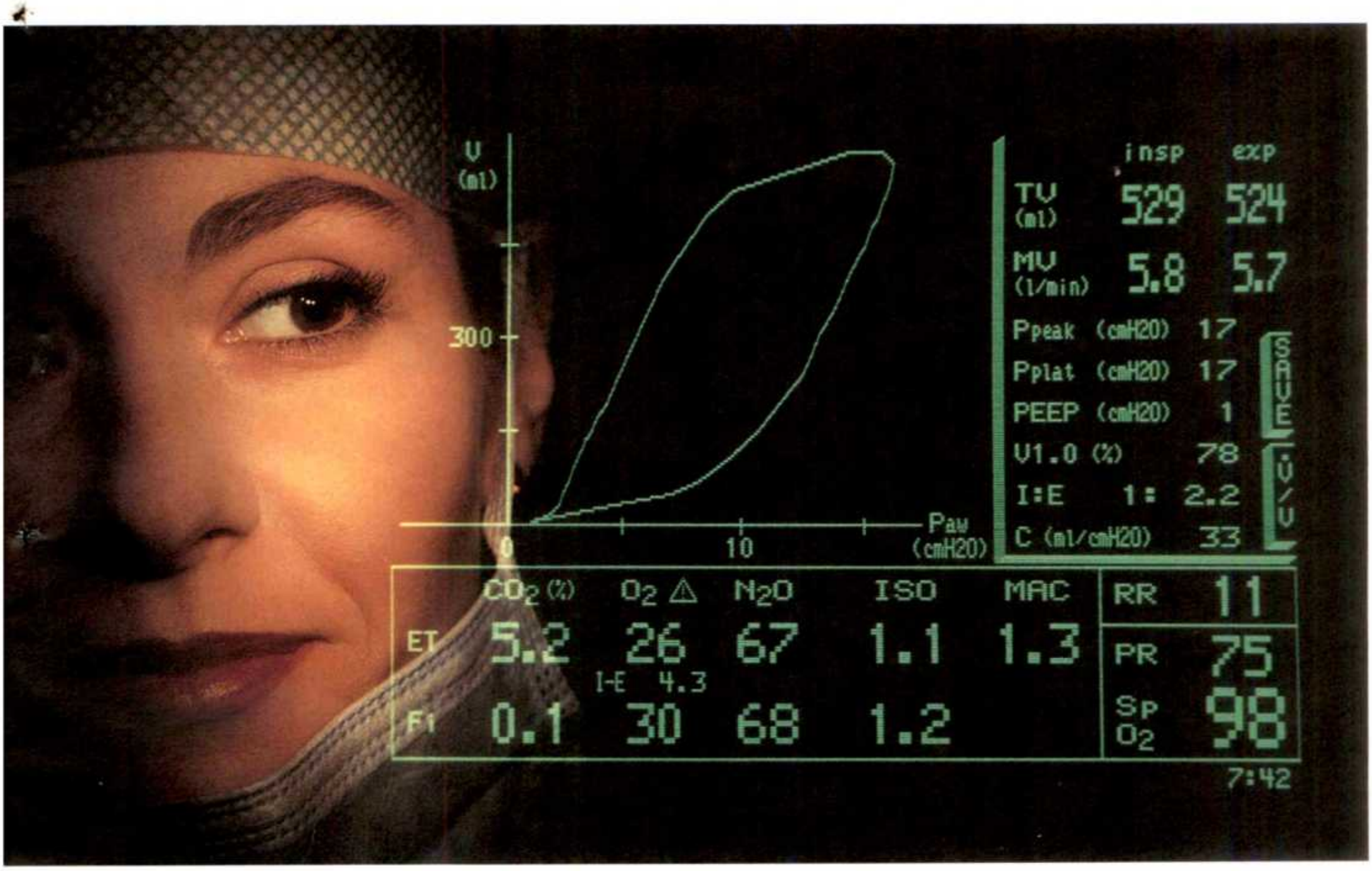

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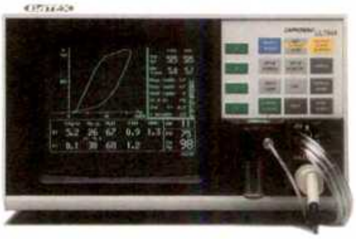

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Brighton November 20–21, 1992

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	Physiology of CPR	M. von Planta (Switzerland)
	Pathophysiology of ischaemic brain injury	K. Hossman (Germany)
Looking Forward	Techniques and strategies for defibrillation	L. Bossaert (Belgium)
	Airway and ventilation care	P. Baskett (U.K.)
	Acid–base disturbances	L. Wiklund (Sweden)
Pharmacotherapy	Drug delivery during CPR	W. Dick (Germany)
	Catecholamines	K. Linder (Germany)
	Antiarrhythmic drugs	D. Chamberlain (U.K.)
Special Situations	CPR in infants and children	D. Zideman (U.K.)
	Hypothermia and near drowning	M. Gilbert (Norway)
	The risks to rescuers	S. Holmberg (Sweden)
National Perspectives	Resuscitation from around Europe	

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ANNUAL MAGILL LECTURE AND SYMPOSIUM: EMERGENCY ANAESTHESIA

London December 10, 1992

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ERRATUM

British Journal of Anaesthesia 1992; **68**: 316–317

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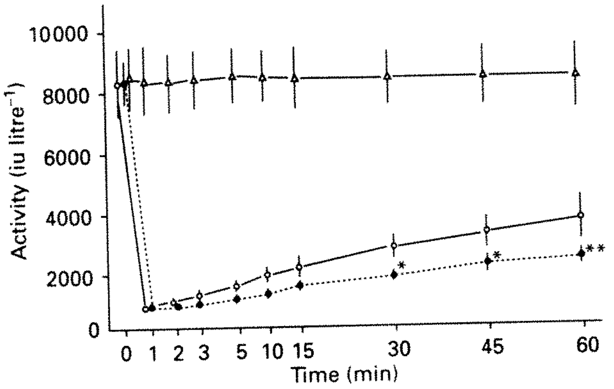

FIG. 1. Mean (SD) erythrocyte acetylcholinesterase activity after administration of neostigmine 0.036 mg kg^{-1} (○), neostigmine 0.071 mg kg^{-1} (●) and edrophonium 1.43 mg kg^{-1} (△). $^{*}P < 0.05$; $^{**}P < 0.01$ compared with neostigmine 0.036 mg kg^{-1}. All values in groups ○ and ● significantly different from baseline ($P < 0.001$).

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Histaminfreisetzung bei der Einleitung von Kombinationsnarkosen mit Nalbuphin oder Fentanyl *

Modulierung der Reaktion durch die Prämedikation Promethazin/Pethidin

W. Dick¹, W. Lorenz², D. Heintz¹, H. Sitter² und A. Doenicke³
¹ Klinik für Anästhesiologie, Johannes Gutenberg-Universität Mainz
² Institut für Theoretische Chirurgie, Philipps-Universität Marburg
³ Institut für Anästhesiologie, Ludwig-Maximilians-Universität München

Zusammenfassung

In einer kontrollierten klinischen Studie an 24 allgemeinchirurgischen Patienten wurde die Histaminkonzentration während der Einleitungsphase einer Kombinationsnarkose mit Nalbuphin (1 mg/kg) oder Fentanyl (5 µg/kg) untersucht. Zur Prämedikation erhielten die Patienten Promethazin (Atosil®) und Pethidin (Dolantin®) 30 min vor den Opioiden. Die Narkoseeinleitung erfolgte mit Alcuronium-Flunitrazepam-Thiopental-Succinylcholin. Nach der Intubation wurde die Analgesie mit Nalbuphin oder Fentanyl aufrechterhalten. Nalbuphin und Fentanyl erwiesen sich als Histaminfreisetzer mit einer mehr als 40%igen Inzidenz. Nalbuphin aber modulierte (potenzierte) noch dazu die Histaminfreisetzung durch die Kombination Alcuronium-Flunitrazepam-Thiopental. Dieser Unterschied zwischen Nalbuphin und Fentanyl war statistisch signifikant (Inzidenz 46% gegen 9%!). Eine direkte Korrelation zwischen Histaminfreisetzung und hämodynamischer Instabilität konnte nicht nachgewiesen werden. Auch eine detaillierte Kausalitätsanalyse mit bedingten Wahrscheinlichkeiten und der Annahme einer beitragenden Determinante für Histamin ergab, daß die Histaminfreisetzung die gemessenen hämodynamischen Parameter kaum beeinträchtigt. Eine mögliche Ursache dieser Ergebnisse besteht in der zeitgerechten vorherigen Gabe von Promethazin, das sowohl eine starke H_1-antagonistische Wirkung wie auch eine H_2-antagonistische Wirkung entfaltet.

Schlüsselwörter

Histamin – Randomisierte Studie – Nalbuphin – Fentanyl – Antihistaminika

Histamine release during induction of anaesthesia with nalbuphine or fentanyl. Modulation of the reaction by premedication with promethazine/pethidine

Abstract

In a controlled clinical trial in patients admitted for general surgery (mainly abdominal and thyroid), histamine release following nalbuphine 1 mg/kg i.v. versus fentanyl 5 µg/kg i.v. was studied in the course of an otherwise routine induction with promethazine/pethidine as premedication 30 min before the opioids and alcuronium - flunitrazepam - thiopental 5 min later. Succinylcholine was given before intubation and further analgesia was obtained by repeated administration of either nalbuphine or fentanyl. Plasma histamine levels were measured by a specific fluorometric assay, heart rate and blood pressure were measured for assessing hemodynamics, and clinical signs of anaphylactoid reactions such as skin eruptions and arrhythmias were registered.

Results. Nalbuphine and fentanyl both released histamine with an incidence of more than 40%. In addition, nalbuphine potentiated the histamine release evoked by the sequential administration of alcuronium-flunitrazepam-thiopental in one complex of application. The incidence of histamine release in the nalbuphine group was 6/13 = 46%, in the fentanyl group only 1/11 = 9% (chi² test, $P < 0.05$). Furthermore, this study showed high histamine levels after succinylcholine and intubation in a relation to time of administration that suggested histamine release as a stress response to intubation. Finally, the incidence of histamine release after a second injection of the opioids was still 30%. A direct correlation between plasma histamine levels, hemodynamic changes, and skin reactions could not be shown. A detailed causality analysis with histamine release as a contributory determinant showed histamine release less detrimental to hemodynamic stability than the opposite, which had been expected. However, the promethazine administered 30 min before induction of anaesthesia had strong H_1- and H_2-receptor antagonistic activity and was given with optimum timing for H_1- and H_2-prophylaxis.

Conclusion. The study demonstrated that histamine release during anaesthesia and surgery depends strongly on the time sequence of drugs and

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CONTENTS

PAGE

EDITORIALS:

I. Interleukin-6 and the metabolic response to surgery 337
G. M. Hall and J. P. Desborough

II. A new look at the breath of life..... 339
M. E. Ward

ORIGINAL ARTICLES

Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy........... 341
J. Joris, I. Cigarini, M. Legrand, N. Jacquet, D. De Groote, P. Franchimont and M. Lamy

Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia 346
P. G. Rabey, P. J. Murphy, J. A. Langton, P. Barker and D. J. Rowbotham

Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis .. 349
R. Jedeikin, D. Olsfanger, D. Shachor and K. Mansoor

Perioperative continuous monitoring of ST-segment changes in patients undergoing elective Caesarean section 352
T. N. Trotter, J. A. Langton, P. Barker and D. J. Rowbotham

EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects 356
G. J. A. Laycock, I. M. Mitchell, R. D. Paton, S. F. O'B. Donaghey, R. W. Logan and N. S. Morton

Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients 363
J. E. Peacock, S. P. W. Spiers, G. A. McLauchlin, W. C. Edmondson, M. Berthoud and C. S. Reilly

I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects of circulatory function... 368
Y. F. Huang, R. N. Upton, A. J. Rutten and W. B. Runciman

Effects of graded infusion rates of propofol on regional and global left ventricular function in the dog....... 375
R. M. Puttick, J. Diedericks, J. W. Sear, J. B. Glen, P. Foëx and W. A. Ryder

Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood–brain barrier 382
A. Werba, H. Gilly, M. Weindlmayr-Goettel, C. K. Spiss, K. Steinbereithner, T. Czech and S. Agoston

REVIEW ARTICLE

One-compartment kinetics 387
J. Norman

SHORT COMMUNICATIONS

A new technique for two-hand bag valve mask ventilation 397
A. N. Thomas, P. T. Dang, J. Hyatt and T. N. Trinh

Tropical anaesthesia for extracorporeal shock wave lithotripsy 399
P. F. McDonald and A. M. Berry

Transient bradycardia associated with extradural blood patch after inadvertent dural puncture in parturients 401
P. J. D. Andrews, W. E. Ackerman, M. Juneja, V. Cases-Cristobal and B. M. Rigor

Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery.. 404
F. Escolano, J. Castaño, R. Lopez, E. Bisbe and A. Alcon

Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway... 407
B. J. Philips, S. Fergusson, P. Armstrong, F. M. Anderson and J. A. W. Wildsmith

Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation . 409
J. C. Berridge

A method to facilitate regional anaesthesia by detection of mixed nerve action potentials 411
M. Y. K. Wee, A. Geeurickx and S. Wimalaratna

CASE REPORTS

Lumbovertebral syndrome after extradural blood patch 414
M. D. Seeberger and A. Urwyler

Accidental subdural catheterization: radiological evidence of a possible mechanism for spinal cord damage 417
I. M. McMenemin, G. R. J. Sissons and P. Brownridge

Life-threatening acute respiratory distress in late pregnancy 420
I. M. Mettam, T. R. Reddy and F. E. Evans

CORRESPONDENCE

Midazolam and cardioversion 422
Delayed septicaemia after extradural steroid treatment. 422
Steroid therapy and extradural analgesia.............. 423
Insulated regional block needles...................... 423
Effect of preoperative opioid administration on postoperative pain 424
Damage to coaxial breathing systems................. 425
Unnecessary preoperative investigations in children.... 425

BOOK REVIEWS

Atlas of Regional Anaesthesia.......................... 426
The Ageing Surgical Patient—Anaesthetic, Operative and Medical Management 426
The Obstructed Airway............................... 427
Adult Respiratory Distress Syndrome.................. 427

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CONTENTS

PAGE

EDITORIALS:

I. Peripheral nerve damage and regional anaesthesia 429
W. A. Chambers

II. The National Confidential Enquiry into Perioperative Deaths 1990 431
S. G. Graham

ORIGINAL ARTICLES

Peripheral nerve injury caused by injection needles used in regional anaesthesia: the influence of bevel configuration, studied in a rat model.................... 433
A. S. C. Rice and S. B. McMahon

Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium 439
C. J. R. Parker, J. M. Hunter and S. L. Snowdon

Etomidate shortens the onset time of neuromuscular block... 444
R. S. Gill and R. P. F. Scott

Disposition of alfentanil in burns patients 447
A. G. Macfie, A. D. Magides and C. S. Reilly

Effect of diclofenac on renal function and prostacyclin generation after surgery............................. 451
I. Power, A. D. Cumming and G. C. Pugh

Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic............. 457
C. H. Blumgart, D. Ryall, B. Dennison and L. M. Thompson-Hill

Comparison of hypertonic saline (5%), isotonic saline and Ringer's lactate solutions for fluid preloading before lumbar extradural anaesthesia................ 461
P. Veroli and D. Benhamou

Cricoid pressure may prevent insertion of the laryngeal mask airway.. 465
J. M. Ansermino and C. E. Blogg

Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? 468
F. R. Ellis, P. J. Halsall and P. M. Hopkins

Evaluation of spin resonance spectroscopy of red blood cell membranes to detect malignant hyperthermia susceptibility 471
P. J. Halsall, F. R. Ellis and P. F. Knowles

Fractional delivery of fresh gas: a new index of the efficiency of semi-closed breathing systems.......... 474
P. C. W. Beatty, G. Meakin and T. E. J. Healy

Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery 478
H. Lange, H. Stephan, C. Brand, S. Zielmann and H. Sonntag

Anaesthesia for critically ill children during magnetic resonance imaging.................................. 482
J. R. Tobin, E. A. Spurrier and R. C. Wetzel

Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat.. 487
J. A. Micol and M. L. Laorden

Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs.................................. 492
B. A. Finegan, R. W. Whiting, Y. K. Tam and A. S. Clanachan

REVIEW ARTICLE

Perioperative blood loss and its reduction: the role of the anaesthestist... 498
P. Simpson

SHORT COMMUNICATIONS

In vitro displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs .. 508
W. R. Williams and D. J. Shale

Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia............. 511
M. Mayer, A. Doenicke, A. Hofmann and K. Peter

CASE REPORTS

Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure....................................... 513
C. Putensen, W. Lingnau, G. Putensen-Himmer and M. Herold

Anaesthesia for Caesarean section in a patient with Ehlers–Danlos syndrome type IV 517
D. Brighouse and B. Guard

Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine 520
B. Tehan

APPARATUS

Bacterial retention properties of heat and moisture exchange filters.................................... 522
M. G. Lee, J. L. Ford, P. B. Hunt, D. S. Ireland and P. W. Swanson

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Leicester Meeting, July 10–11, 1992 .... 526P

CORRESPONDENCE

Retrograde intubation using the subcricoid region 542
Ventilatory effects of laparoscopy under general anaesthesia 542
European Standardization Committee on Anaesthetic Equipment 543
Radioimmunoassay tests and anaphylaxis 543
Respiratory depression after extradural fentanyl 544
A puncture technique for continuous subarachnoid block... 544
Bacterial overgrowth and gastric dysfunction 545

BOOK REVIEWS

Emergency Medicine and the Anaesthetist.............. 546
MCQ for Higher Examinations in Clinical Pharmacology 546
Clinical Practice of Regional Anesthesia 546
Maternal Mortality—The Way Forward. Some Implications of the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–87 547
Critical Care Toxicology.............................. 547
Manual of Obstetric Anesthesia, 2nd Edn 547
The Management of Acute Pain........................ 548
The Critical Care Drug Handbook 548

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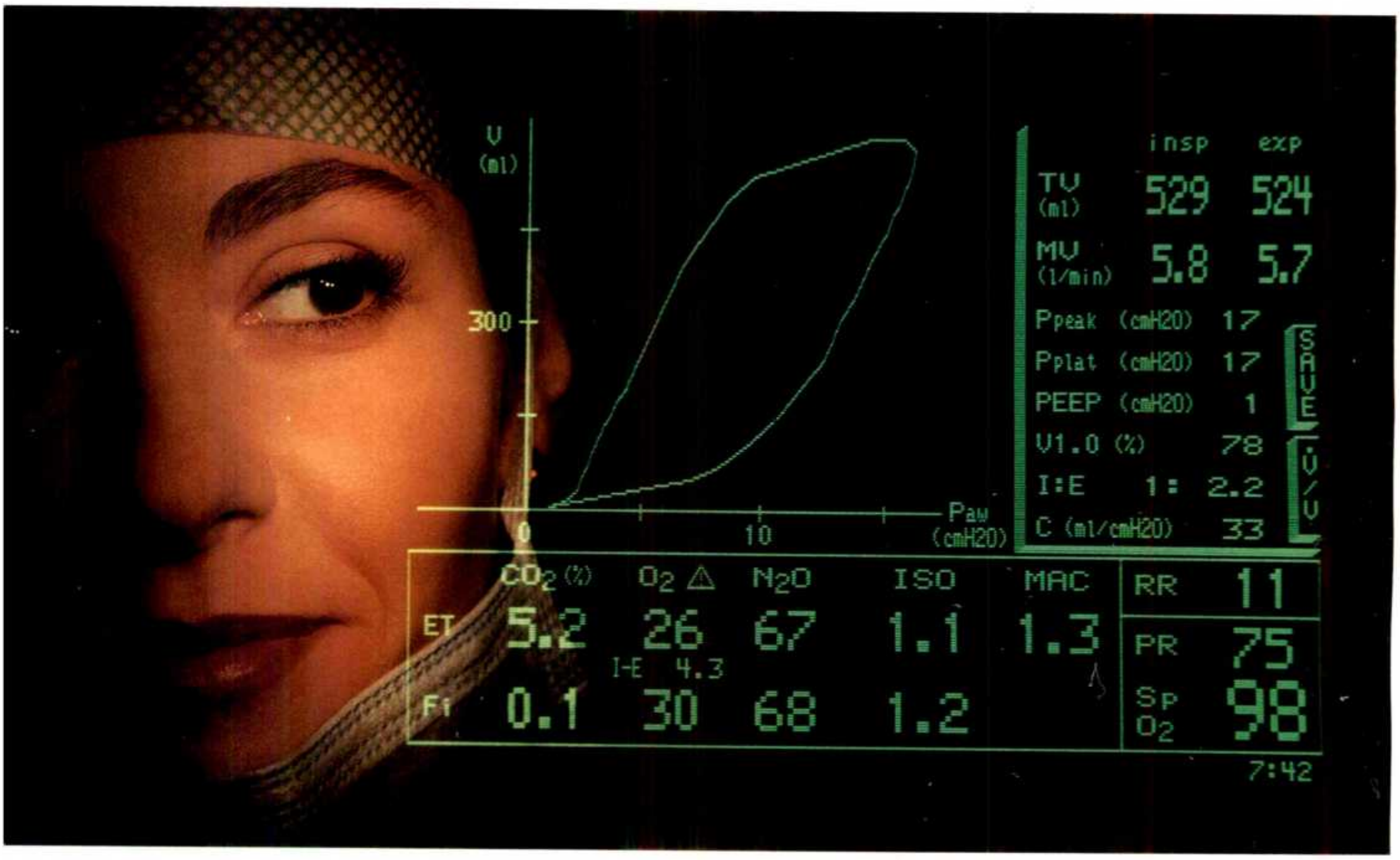

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CONTENTS

PAGE

EDITORIAL: The era of relaxant anaesthesia 551
J. E. Utting

ORIGINAL ARTICLES

Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia 554
T. H. Madej, R. G. Wheatley, I. J. B. Jackson and D. Hunter

Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia 558
R. G. Wheatley, D. Shepherd, I. J. B. Jackson, T. H. Madej and D. Hunter

Effects of isoflurane anaesthesia on the median nerve somatosensory evoked potential in children 562
D. G. Mason, D. Higgins, S. G. Boyd and A. R. Lloyd-Thomas

Sequential measurement of the median nerve somatosensory evoked potential during isoflurane anaesthesia in children 567
D. G. Mason, D. Higgins, S. G. Boyd and A. R. Lloyd-Thomas

Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia 570
B. L. Browne, C. Prys-Roberts and A. R. Wolf

Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery 577
S. Michael, I. Barker, P. Henderson, R. W. Griffiths and C. S. Reilly

Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure 580
D. R. Cook, J. A. Freeman, A. A. Lai, Y. Kang, R. L. Stiller, S. Aggarwal, J. C. Harrelson, R. M. Welch and B. Samara

Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum 586
Z. Esener, B. Sarihasan, H. Güven and E. Üstün

Spinal anaesthesia for Caesarean section: comparison of 22-gauge and 25-gauge Whitacre needles with 26-gauge Quincke needles 589
L. E. Shutt, S. J. Valentine, M. Y. K. Wee, R. J. Page, A. Prosser and T. A. Thomas

Effect of fentanyl on ventilatory resistances during barbiturate general anaesthesia 595
R. Cohendy, J. Y. Lefrant, M. Laracine, T. Rebiere and J. J. Eledjam

Accuracy of coagulation studies performed on blood samples obtained from arterial cannulae 599
S. R. Haynes, W. Allardyce, B. Cowan and P. Tansey

Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery 602
K. D. Stühmeier, B. Mainzer, W. Sandmann and J. Tarnow

Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma 607
S. Chaudhri, J. R. Colvin, J. G. Todd and G. N. C. Kenny

Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs 611
D. Laroche, C. Lefrançois, J.-L. Gérard, F. Dubois, M.-C. Vergnaud, J.-L. Guéant and H. Bricard

Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin $F_{2\alpha}$ in human pial arteries 615
P. Reinstrup, T. Uski and K. Messeter

REVIEW ARTICLE

Massive blood transfusion 621
M. D. J. Donaldson, M. J. Seaman and G. R. Park

SHORT COMMUNICATIONS

Retrograde intubation—a facilitated approach 631
S. S. Dhara

Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour 634
S. McHale, V. Mitchell, S. Howsam and F. Carli

Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy 637
M. Welte, E. Haimerl, J. Groh, J. Briegel, L. Sunder-Plassmann, A. Herz, K. Peter and C. Stein

An active heat and moisture exchanger 640
F. Kapadia, M. P. Shelly, J. M. Anthony and G. R. Park

Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol 643
J. M. Murray and T. R. Trinick

CASE REPORTS

Apparent pacemaker failure caused by activation of ventricular threshold test by a magnetic instrument mat during general anaesthesia 645
J. P. Purday and R. M. Towey

Extradural abscess complicating extradural anaesthesia for Caesarean section 647
W. D. Ngan Kee, M. R. Jones, P. Thomas and R. J. Worth

General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients 653
G. Samsoon, M. E. Wood, A. B. Knight-George and R. P. Britt

Use of suction catheters as an alternative to tracheal tubes in adults 657
P. S. Gataure, I. P. Latto and H. Taylor

COMMENTARY

Guest reviewers for 1992 659

CORRESPONDENCE

Hypoxaemia and insertion of the laryngeal mask airway 661
Vocal cord movement on induction of anaesthesia 661
Spinal anaesthesia for Caesarean section 662
Metallic fragments and the combined spinal-extradural technique 662
Inspiratory to end-tidal oxygen difference 663
Pre-emptive extradural analgesia 663
Skin injury with a pulse oximeter 665

BOOK REVIEWS

Respiratory Monitoring (Contemporary Management in Critical Care series) 666
Principles of Measurement and Monitoring in Anaesthesia and Intensive Care, 3rd Edn 666
Anaesthesia for Ophthalmic and Otolaryngologic Surgery 667
Kinetics of Anaesthetic Drugs in Clinical Anaesthesiology 667
MCQ Companion to the Textbook of Anaesthesia 667
Plasma Volume Expansion 668

Index to Volume 69 669

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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL I

INTERLEUKIN-6 AND THE METABOLIC RESPONSE TO SURGERY

Surgery evokes a wide variety of metabolic changes including increased thermogenesis, hyperglycaemia, loss of muscle protein, acute phase protein synthesis, a decrease in the plasma divalent cations iron and zinc and an increased white cell count. The main causes of the metabolic response are thought to be afferent neuronal input from the operative site, both somatic and autonomic, and the release of cytokines from damaged tissue resulting from surgical trauma. Anaesthetists have concentrated their efforts in trying to understand the former causative factor and there is general agreement that complete afferent neuronal block of the operative site prevents the classical catabolic hormonal response. Unfortunately, complete neuronal block can be achieved only for surgery of the limbs, pelvic organs and the eye. When this is achieved, however, the inhibition of catabolic hormone secretion results in a marked effect on some aspects of the metabolic response, such as prevention of the hyperglycaemia, but has no impact on other areas such as acute phase protein synthesis [1]. It is likely that, with the recent explosive increase in knowledge of the cytokines, a complete understanding of the causation of the metabolic response to surgery will become clear.

The cytokines are a large, and rapidly expanding, group of polypeptides. This group includes the interleukins (IL1-12 so far), tumour necrosis factor (TNF α and β) and the interferons. The cytokines have numerous effects on a wide variety of tissues, particularly immunological cells. The major sites of synthesis of the cytokines are cells of the macrophage and monocyte series, but synthesis has been described in many other types such as fibroblasts and glial cells. Anaesthetic interest has focused mainly on TNF α and IL-I_{β}, as both have been implicated as mediators of the "sepsis syndrome" [2], and there have been preliminary trials to examine any potential benefits from blocking their actions [3]. There are many interactions between the cytokines, for example TNF α induces IL-I expression and both can stimulate production of IL-6.

Interleukin-6 is the main cytokine released after routine surgery; circulating IL-I_{β} and TNF α values do not increase. Cruickshank and colleagues have shown that the increase in concentration of circulating IL-6 is approximately proportional to the severity of the surgery [4]. Furthermore, they were able to demonstrate a good correlation between the increase in circulating IL-6 values and the increase in serum C-reactive protein (CRP). This association was not surprising, as one of the many names given previously to IL-6 was hepatocyte stimulating factor. Other synonyms for IL-6 include B cell stimulatory factor-2, interferon β_2, 26 kDa protein, hybridoma–plasmacytoma growth factor and myeloid blood cell differentiation-inducing protein. The biochemical and immunological aspects of IL-6 have been reviewed [5, 6]. The structure of the IL-6 gene, the sequence of the 23 kDa polypeptide and the IL-6 receptor have all been elucidated. However, the method of signal transduction after stimulation of the IL-6 receptor is unclear. Interleukin-6 not only stimulates acute phase protein synthesis in the liver, but also has effects on the immune system and haematopoiesis. These include B cell proliferation and T differentiation, T cell costimulation and plasmocyte proliferation. A possible role in the control of anterior pituitary hormone secretion has also been suggested [7].

This issue of the Journal contains an article by Joris and colleagues in which the authors have compared the hormonal and metabolic responses to cholecystectomy conducted by either conventional laparotomy or laparoscopy [8]. Although some aspects of the study design were questionable, for example historical controls were used for the laparotomy group, nevertheless the data offer some useful clues to the role of IL-6 in mediating the metabolic response to surgery.

The authors found that the duration of hospital stay was reduced by nearly 50% in the patients operated on laparoscopically (2.75 days *vs.* 5.0 days), although the duration of surgery was longer (121 min *vs* 96 min). The improved recovery in the laparoscopy group was associated with a decreased duration of postoperative fasting, an improvement in simple respiratory function tests and a decrease in analgesic consumption (although pain scores were similar in the two groups, probably because analgesics were readily available). The IL-6 results showed a significantly decreased response in the laparoscopy group throughout the study and this was associated with a decrease in circulating concentrations of CRP and white blood cell count. The improvement in the IL-6 response confirms the original observation of Cruickshank and colleagues [4] that tissue damage is a major determinant of the circulating value of this cytokine. Changes in plasma adrenaline, noradrenaline and cortisol concentrations were comparable throughout the study in the two groups and this emphasizes the importance of the IL-6 related changes in determining rate of recovery from surgery. It is interesting to note that the amount of volatile anaesthetic required was similar also in the laparoscopy and laparotomy groups. These findings suggest that visceral afferent stimulation is the main factor in stimulating the neuro-

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endocrine response to surgery. The hormonal and cytokine data of Joris and colleagues [8] require confirmation by other groups, although there is already general agreement that recovery is more rapid after uncomplicated laparoscopic surgery.

It is tempting to extrapolate these interesting results to the area of regional anaesthesia and speculate about their biological importance. As discussed previously, complete afferent neuronal block can prevent the classical neuroendocrine response to surgery only at certain specific operative sites. Even when abolition of this response has been achieved, little benefit in postoperative morbidity has been shown [9], in spite of occasional claims to the contrary [10]. We have shown recently that an extradural block from the T4–S5 dermatomes for pelvic surgery had no effect on circulating IL-6 concentrations, although anterior pituitary hormone secretion was prevented and catecholamine-mediated metabolic changes were blocked [11]. Is the failure of regional anaesthesia to improve postoperative recovery caused by inability to alter the IL-6 response and hence cytokine-mediated changes? Are the classical hormonal markers of surgical trauma largely irrelevant as determinants of outcome? The answers to these and similar questions will be pursued energetically over the coming years. The unravelling of the role of cytokines as mediators of metabolic, immunological, haematological and possibly hormonal responses to surgery offers an exciting challenge to anaesthetists to marry the findings of basic science to important epidemiological questions in clinical anaesthesia.

G. M. Hall and J. P. Desborough
London

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EDITORIAL II

A NEW LOOK AT THE BREATH OF LIFE

One problem encountered by professionals and experts is understanding the difficulties of the novice in acquiring practical skills. This difficulty is exemplified in particular by the problems experienced by the beginner in maintaining an airway and ventilating with a bag valve mask (BVM) system [1]. Several techniques have been recommended and devices developed in recent years to overcome some of these difficulties, but it is only recently that the problem has been recognized adequately in the area of basic life support. Indeed, at the recent American Heart Association meeting at Dallas, in February 1992, whilst intubation was again confirmed as the gold standard for airway care in resuscitation, it was finally agreed that BVM should be carried out by *two* persons. Furthermore, at this meeting, the oesophageal obturator airway was relegated to a "not recommended" status, and the simple pocket mask with jaw-tug/head-tilt was recognized again as being more effective at maintaining an adequate airway and permitting ventilation than the BVM system [2]. This is a welcome move to simplicity in an increasingly "high-tech" situation!

Alternatives to tracheal intubation are also now being introduced for lesser trained personnel, in an effort to overcome some of the difficulties of ventilation and airway care. It has been suggested that the paramedic services could be trained more rapidly and with greater efficiency to use the Brain laryngeal mask airway [3]. Newer items of equipment, more reliable but slightly more daunting in appearance, are making a play to fill the void left by the oesophageal obturator airway. The so called pharyngeal–tracheal lumen airway (PTLA) [4] and the oesophageal tracheal combitube (ETC) [5, 6] are two variations on the concept of the oesophageal airway. Both of these devices have as their rationale the avoidance of any need to lift the jaw–tongue unit forwards; in theory, both allow effective ventilation, whether it is the oesophagus or the trachea that is intubated. They also both rely on blind intubation of either the oesophageal or tracheal orifices. In the area of trauma management additionally, they have the advantage of requiring minimal neck movement. However, in common with the Brain laryngeal mask airway, these devices do not give the degree of tracheal protection provided by the tracheal tube. It could be that, in the future, these tubes may have a place in our armamentarium, but the nature of that place has not yet been defined.

There are many older airway support and ventilation devices. The Brook airway was described originally in 1962 [7] and showed great foresight in providing rescuer protection with a non-return valve. However, its high air flow resistance for both rescuer and victim and its difficulty in use [8] led to the Resuscitation Council recommending the discontinuation of its use. The Guedel Airway has weathered the test of time better, having been introduced in 1933 [9], and being recommended still for use by correctly trained medical and paramedical personnel, even today.

There is no doubt that it will be many years before the BVM assembly is discarded in all British hospitals as the first line ventilation device for patients during the earliest phase of a cardiac arrest. This is particularly true with the increasing anxiety about close personal contact as a result of the recent HIV and hepatitis B controversies. It is encouraging, therefore, that this form of ventilation is increasingly the subject of critical study [10], including the paper from the University of California in this edition of the Journal [11]. The only problem that the authors of the latter paper have not addressed is the difficulty in maintaining an open airway with one hand when ventilating with the other, compared with using two hands to control the airway and another two hands to squeeze the bag. It is this aspect of the BVM ventilation technique which causes the most difficulty, and it is for this reason that the Resuscitation Council of the United Kingdom recommends that, when only one rescuer is available, a pocket mask be utilized, maintaining the airway with two hands, rather than the bag valve mask assembly. However, with the pocket mask the optimal position for the rescuer is from the head of the patient which, with a single rescuer, may marginally delay the application of chest compression. This continuing interest in basic life support techniques is welcome and is preferable to simple anecdotal reports.

M. E. Ward
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ORIGINAL ARTICLES

METABOLIC AND RESPIRATORY CHANGES AFTER CHOLECYSTECTOMY PERFORMED VIA LAPAROTOMY OR LAPAROSCOPY

J. JORIS, I. CIGARINI, M. LEGRAND, N. JACQUET, D. DE GROOTE,
P. FRANCHIMONT AND M. LAMY

SUMMARY

*We have compared metabolic and respiratory changes after laparoscopic cholecystectomy (*n *= 15) with those after open cholecystectomy (*n *= 15). The durations of postoperative i.v. therapy, fasting and hospital stay were significantly shorter in the laparoscopy group. During the first and second days after operation, analgesic consumption but not pain scores (visual analogue scale) were significantly smaller after laparoscopy, while vital capacity, forced expiratory volume in 1 s, and* Pa_{O_2} *were significantly greater. The metabolic and acute phase responses (glucose, leucocytosis, C-reactive protein) were less after laparoscopy compared with laparotomy. Although plasma cortisol and catecholamine concentrations were not significantly different between the two groups, after surgery interleukin-6 concentrations were less in the laparoscopy group.*

KEY WORDS

Lung: postoperative function. Metabolism: acute phase reaction. Pain: postoperative. Surgery: cholecystectomy, laparoscopic surgery.

Laparoscopic cholecystectomy is said to have many advantages [1–2] compared with the open operation, the major one being a shorter duration of hospital stay [3]. Upper abdominal surgery is followed by several side effects: pain, pulmonary dysfunction and endocrine and metabolic changes. It is conceivable that the faster recovery and feeling of well-being described after laparoscopic compared with open cholecystectomy might reflect better maintenance of homeostasis. However, no studies have examined this area [4].

We have therefore compared postoperative pain, pulmonary dysfunction and endocrine and metabolic changes after cholecystectomy performed by either laparotomy or laparoscopy.

PATIENTS AND METHODS

We studied 30 patients, ASA grades I and II, undergoing elective cholecystectomy, after local Ethics Committee approval and informed patient consent had been obtained. None of the patients had acute cholecystitis. Fifteen patients underwent laparoscopic cholecystectomy and the data obtained were compared with those from 15 previously investigated [5] patients who underwent laparotomy via a subcostal incision. All pre-, intra- and post-operative conditions other than the surgical approach (surgeons, anaesthetists, nurses, observers) were similar for the two groups (table I). All operations were performed in the morning after an approximate preoperative fast of 8 h.

All patients were premedicated with hydroxyzine 50–75 mg orally 2 h before surgery and an i.m. injection of midazolam 5 mg and atropine 0.25 mg just before transfer to the operating theatre. Anaesthesia was induced with sufentanil 15–20 μg, thiopentone 5 mg kg^{-1} and atracurium 0.5 mg kg^{-1}. After tracheal intubation, general anaesthesia was maintained with 50 % nitrous oxide in oxygen and isoflurane as needed. The duration of surgery (time elapsed from the end of the induction of anaesthesia until skin closure) and the mean end-tidal concentration of isoflurane (Datex Capnomac) were recorded. During laparoscopic procedures, intra-abdominal pressure was maintained automatically at 14 mm Hg by a carbon dioxide insufflator (Wolf 2154.201). Patients were placed in a 10° head-up position. During surgery, all patients received an i.v. infusion of lactated Ringer's solution. After surgery, a 5 % glucose solution was infused at a rate of 80 ml h^{-1}.

Pain assessment

Pain score was assessed using a 100-mm visual analogue scale [6] when patients requested analgesic medication, 4 h after the end of surgery, at 08:00, 14:00 and 20:00 on day 1 and at 08:00 on day 2. Both groups received i.m. injections of piritramide 0.2 mg kg^{-1} 4 hourly as required and the consumption was recorded during the first 48 h. Patients from both groups received the same information from the

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This article is accompanied by Editorial I.

J. JORIS, M.D., I. CIGARINI, M.D., M. LAMY, M.D. (Department of Anaesthesiology); M. LEGRAND, M.D., N. JACQUET, M.D. (Department of Surgery); P. FRANCHIMONT, M.D. (Department of Endocrinology); University Hospital, of Liège, B-4000 Sart Tilman, Belgium. D. DE GROOTE, PH.D., Medgenix Group, Fleurus, Belgium. Accepted for Publication: March 27, 1992.

Correspondence to J.J.

TABLE I. *Patient characteristics and details of hospital stay (mean (range or* SEM*)).* *$P < 0.05$ *between groups*

	Laparoscopy ($n = 15$)		Laparotomy ($n = 15$)
Age (yr)	46.0 (22–65)		51.8 (29–70)
Weight (kg)	71.4 (3.7)		74.7 (3.5)
Height (cm)	164.7 (2)		168.0 (2.4)
Sex (F/M)	12/3		9/6
Duration of surgery (min)	121 (10)		96 (11)
Isoflurane (%)	0.86 (0.05)		0.83 (0.07)
Duration of postop. i.v. infusion (h)	20.6 (2.85)	*	40.3 (3.33)
Duration of postop. fasting (h)	16.1 (2.17)	*	29.17 (3.33)
Duration of postop. hospital stay (day)	2.75 (0.16)	*	5.0 (0.25)

same anaesthetist (J.J.) and nurses concerning analgesic availability. Piritramide 20 mg has been shown to be equianalgesic with morphine 15 mg [7].

Pulmonary function

Pulmonary function was measured by the same technician with the patient in a semi-sitting position before surgery, 4 h after the end of surgery and 2 days after surgery, using a Gould Pulmonet III. Patients were kept in this position for 20 min before testing without supplementary oxygen. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), ventilatory frequency (f), tidal volume (V_T) were measured and the greatest value of three attempts was recorded. Arterial blood samples were obtained by femoral artery puncture for blood-gas analysis, just before pulmonary function testing.

Endocrine and metabolic responses

Blood samples were obtained from an antecubital vein before surgery, 4 h after the end of surgery and on days 1 and 2 at 08:00. Plasma concentrations of glucose, C-reactive protein (CRP), cortisol, catecholamines and interleukin-6 (IL-6) and leucocyte counts were measured, by technicians blinded to the type of surgery.

Serum concentration of CRP was measured by laser nephelometry (Behring, Marburg, Germany). The sensitivity of the assay was 2.5 mg $litre^{-1}$ and intra-assay and interassay coefficients of variation were 2.3% and 10%, respectively.

Plasma concentration of total cortisol was measured by direct radioimmunoassay [8]. The sensitivity of the assay was 25 nmol $litre^{-1}$. All assays were processed in duplicate with maximal 4.3% intra-assay and 8.3% interassay coefficients of variation.

Plasma concentrations of adrenaline and noradrenaline were measured using high-pressure liquid chromatography with electrochemical detection [9]. Sensitivity of these two assays was 0.02 nmol $litre^{-1}$. Intra- and interassay coefficients of variation were 7.4% and 9.8%, respectively.

IL-6 was measured by a two-step immunoradiometric assay (IRMA) using a prototype from Medgenix (Fleurus, Belgium) [10]. Briefly, the two-step IRMA is based on coated-tube separation and on an oligoclonal system in which several monoclonal antibodies are directed against distinct epitopes of IL-6. The captured antibodies are attached to the lower and inner surface of plastic tubes which are provided in the kit. The IL-6 concentration of samples was determined by interpolation using a standard curve prepared at the same time. The sensitivity of this IRMA was 5 pg ml^{-1}. Intra- and interassay variability were 5.6% and 7.5%, respectively. The recovery test showed an 89% recovery. Normal values are < 10 pg ml^{-1}.

Statistical analysis

Results are reported as mean (SEM). Time-dependent variables in the treatment groups were compared by Zerbe's method [11]. This technique allows one to test the hypothesis of the equality of response curves for two or more groups at each time or during any given time interval. It uses an F-test in which the degrees of freedom depend not only on the group sample sizes, but also on the time period chosen. Student's t test was also used when appropriate. Correlation between CRP and IL-6 concentrations was tested for significance by linear regression. All results were considered to be statistically significant at the 5% level.

RESULTS

Both groups were comparable except for the sex ratio (table I). The duration of surgery for laparoscopy was longer than that for laparotomy (ns: $P = 0.07$) (table I). The mean end-tidal concentration of isoflurane needed to keep the patient haemodynamically stable during surgery was similar with both surgical techniques: approximately 0.85%. In contrast, duration of postoperative i.v. infusion, postoperative fasting and hospital stay were significantly shorter in the laparoscopy group ($P < 0.05$).

Pain and analgesic consumption

Pain reported immediately after surgery was less intense after laparoscopy than after laparotomy (ns: $P = 0.19$) (fig. 1). The duration of pain was shorter in the laparoscopy group (see day 2) and pain scores were more variable in the laparoscopy group. Overall, pain intensity did not differ significantly between the two groups ($P = 0.17$). However, on day 2, pain was negligible after laparoscopy and significantly less than after laparotomy ($P < 0.05$).

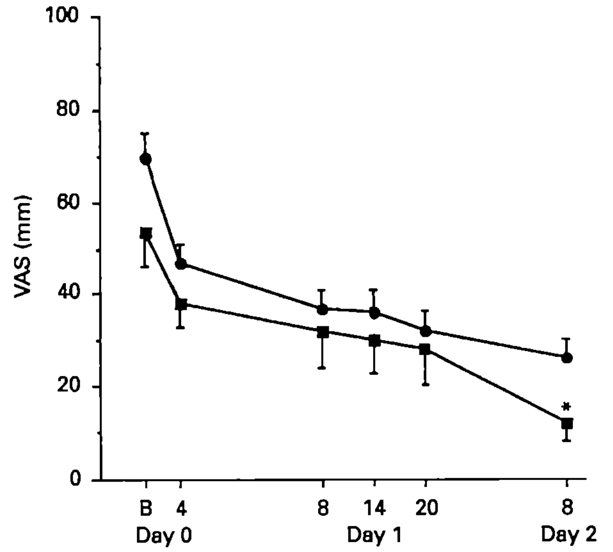

FIG. 1. Pain scores (mean, SEM) after cholecystectomy by laparoscopy (■) and laparotomy (●). Pain was assessed before administration of analgesia (Day 0: B), 4 h after the end of surgery (Day 0: 4) on day 1 at 08:00 (8), 14:00 (14) and 20:00 (20) and on day 2 at 08:00 (8). $*P < 0.05$ between groups.

Although pain was similar in both groups at most time points, a two-fold reduction in analgesic consumption was observed after laparoscopy during the first and second days (first day: piritramide 0.22 (SEM 0.04) mg kg^{-1} *vs* 0.37 (0.03) mg kg^{-1} ($P < 0.05$); second day: piritramide 0.06 (0.04) mg kg^{-1} *vs* 0.24 (0.04) mg kg^{-1} ($P < 0.05$)). Whereas four of 15 patients requested analgesic on the second day in the laparoscopy group, 12 of 15 requested it in the laparotomy group. After laparotomy, patients complained more of parietal pain (abdominal wall), whereas after laparoscopy patients reported visceral pain similar in location and type to biliary colic, and shoulder-tip pain secondary to diaphragmatic irritation.

Pulmonary function

After surgery, FVC and FEV_1 decreased in both groups (table II). Tidal volume decreased, but minute ventilation was unchanged because of a compensatory increase in ventilatory frequency. After laparoscopy, the reductions in FVC and FEV_1 were not as pronounced as after laparotomy ($P < 0.05$). Two days after laparoscopy, patients had a greater Pa_{O_2} than those who had laparotomy ($P < 0.05$).

Endocrine and metabolic responses

Before operation, endocrine and metabolic variables were similar in both groups. In particular, median serum concentrations of IL-6 in the two groups were < 5 pg ml^{-1}—the assay detection limit. Serum concentrations of cortisol increased after operation at 4 h and returned to normal values on day 1, with no significant difference between the two groups at any time (fig. 2). Plasma concentrations of catecholamines did not differ significantly between the two groups (fig. 2). IL-6 was released during the postoperative period; at 4 h, the serum concentration was significantly less after laparoscopy ($P < 0.05$) (fig. 2). Plasma concentrations of glucose and CRP, and leucocyte counts increased in both groups after surgery, but the values were significantly smaller and of shorter duration in the laparoscopy group ($P <$ 0.05) (fig. 3). There was a linear correlation between the peak concentrations of IL-6 and CRP ($r = 0.64$, $P < 0.05$).

DISCUSSION

Surgery is associated with metabolic and acute phase responses characterized by clinical and biological events: hyperglycaemia, leucocytosis, fever and production of acute phase proteins, such as CRP, by the liver [12]. The acute phase reaction, and more particularly the serum concentration of CRP, reflect the amount of tissue damage [13] and the severity of illness [14]. We have shown that this acute phase reaction was significantly reduced after laparoscopic cholecystectomy than that after laparotomy. The different glycaemic responses of the two groups were not caused solely by the shorter duration of fasting and infusion of 5% glucose in the laparoscopy

TABLE II. *Pulmonary function before surgery (Pre.), 4 h after operation (4 h) and on day 2 after cholecystectomy performed via laparoscopy or laparotomy (mean (SEM)). FVC = Forced vital capacity; FEV_1 = forced expiratory volume in 1 s;* V_T = *tidal volume*; f = *ventilatory frequency.* $*P < 0.05$ *between groups*

	Pre.	4 h	Day 2
FVC (ml)			
Laparoscopy	3073 (173)	2150 (216)	2600 (192)
Laparotomy	3291 (167)	1522 (131)*	1946 (111)*
FEV_1 (ml s^{-1})			
Laparoscopy	2342 (141)	1600 (190)	1992 (150)
Laparotomy	2331 (164)	969 (110)*	1400 (106)*
V_T (ml)			
Laparoscopy	615 (30)	429 (23)	500 (30)
Laparotomy	631 (39)	428 (28)	503 (49)
f (b.p.m.)			
Laparoscopy	14 (1)	16 (1)	15 (1)
Laparotomy	14 (1)	16 (1)	14 (1)
Pa_{O_2} (kPa)			
Laparoscopy	12.4 (0.53)	10.5 (0.48)	11.2 (0.55)
Laparotomy	11.8 (0.35)	10.0 (0.27)	10.1 (0.44)*
Pa_{CO_2} (kPa)			
Laparoscopy	4.7 (0.13)	5.0 (0.13)	4.8 (0.16)
Laparotomy	4.8 (0.11)	4.9 (0.16)	5.0 (0.11)

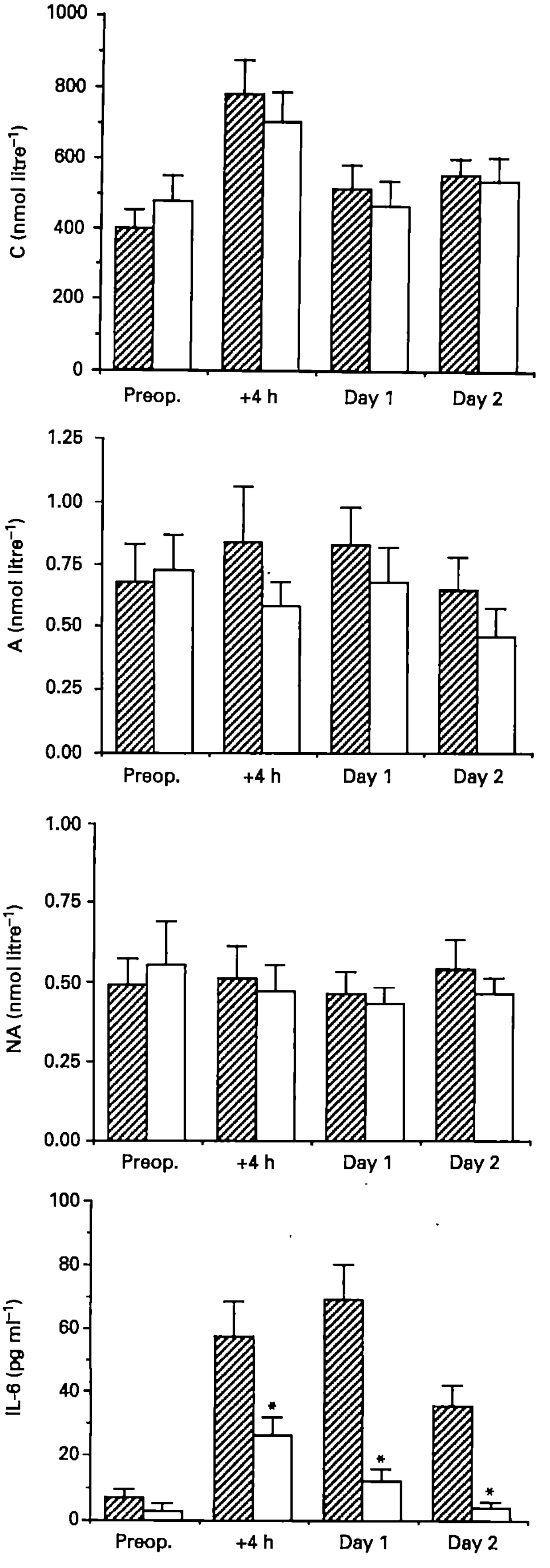

FIG. 2. Neuroendocrine response and interleukin-6 (IL-6) release (mean, SEM) after cholecystectomy by laparotomy (▨) and by laparoscopy (☐). Samples were taken before surgery (Preop.), 4 h after surgery (+4 h), and on days 1 and 2 (at 08:00). C = Cortisol; A = adrenaline; NA = noradrenaline. Comparison of the two response curves for IL-6: $F = 18.99$, $P < 0.05$. $^*P < 0.05$ between groups.

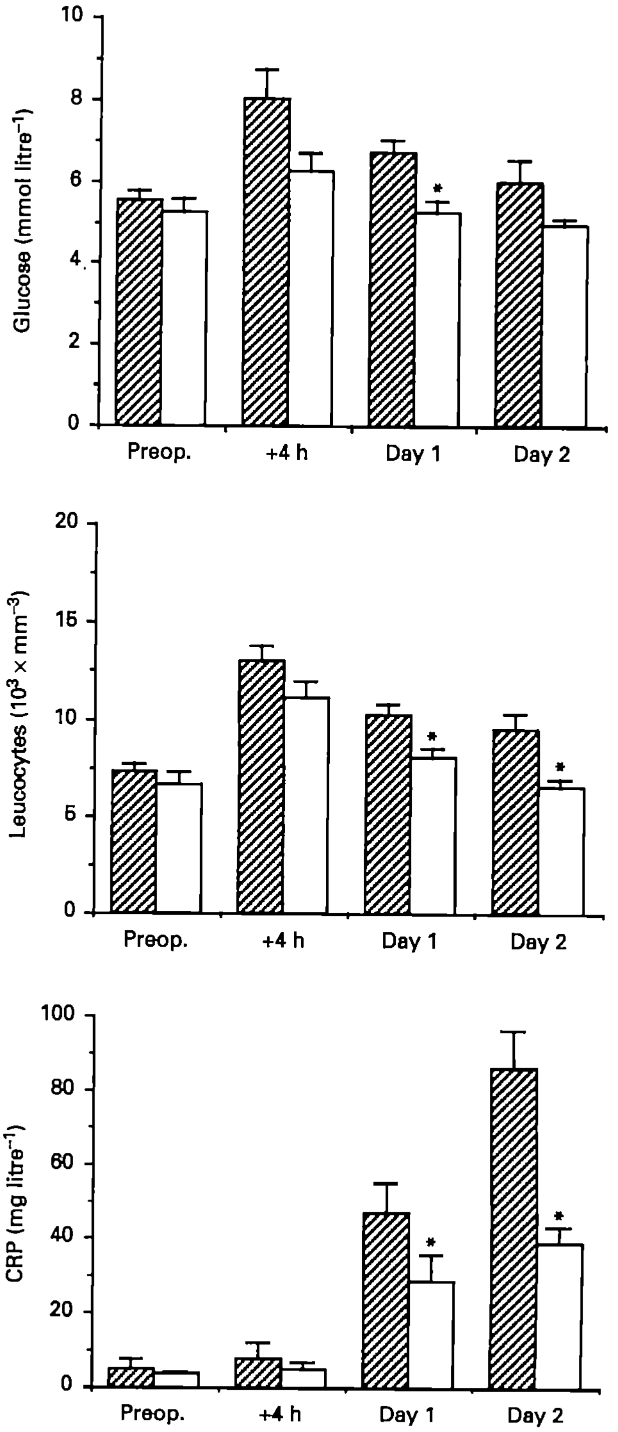

FIG. 3. Metabolic and acute phase responses (mean, SEM) after cholecystectomy by laparotomy (▨) and by laparoscopy (☐), measured before surgery (Preop.), 4 h after surgery (+4 h), and on days 1 and 2 (at 08:00). CRP = C-reactive protein. Comparison of the two response curves for glucose: $F = 6.13$, $P < 0.05$; for leucocytes: $F = 5.87$, $P < 0.05$; for CRP: $F = 12.70$, $P < 0.05$. $^*P < 0.05$ between groups.

group. Ten of the 15 patients in this group still had an infusion in progress on day 1 at 08:00. Using only these 10 patients, the differences between the two groups at the first three sampling times remained statistically significant ($F = 6.63$; $P < 0.05$).

The metabolic response is mediated by neuroendocrine stimulation in addition to release of inflammatory mediators (cytokines) from the surgical wound [15]. One of these cytokines, interleukin-6, is activated by tissue trauma, and appears to be the most efficient stimulator of hepatic acute phase protein production [16, 17]. Increases in IL-6 concentrations were significantly smaller after laparoscopy than after laparotomy ($P < 0.05$), and there was good correlation between peak concentrations of IL-6 and CRP. In contrast, the observation that plasma concentrations of cortisol and catecholamines were not significantly different between the two groups suggests that the neuroendocrine stimulation induced by the two surgical procedures was similar. However, overall, our results provide biochemical evidence that the extent of surgical trauma was less for laparoscopic than for open cholecystectomy.

A reduction in surgical trauma has economic and clinical consequences. Postoperative fasting, duration of i.v. infusion and hospital stay were significantly less after laparoscopy than after laparotomy. Surgical trauma contributes to pain and pulmonary dysfunction. After laparoscopic cholecystectomy, pain was not significantly less than after laparotomy except on day 2. However, consumption of opioids to attain similar degrees of analgesia was significantly less after laparoscopy. The duration of pain after laparoscopic cholecystectomy was shorter, as indicated not only by the reduced pain score on day 2, but also by the reduction in requests for opioids.

The postoperative changes in pulmonary function were typical of upper abdominal surgery [18]. Our findings confirm that laparoscopic cholecystectomy results in less respiratory dysfunction than laparotomy [19]. Whereas FVC and FEV_1 differed markedly in the two groups, at both postoperative observation times, differences in Pa_{O_2} were less obvious. The lack of significant difference in relative hypoxaemia measured at 4 h, in spite of a marked difference in pulmonary dysfunction, might be a reflection of sedation secondary to residual effects of anaesthesia and opioids, in addition to pain.

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EFFECT OF THE LARYNGEAL MASK AIRWAY ON LOWER OESOPHAGEAL SPHINCTER PRESSURE IN PATIENTS DURING GENERAL ANAESTHESIA

P. G. RABEY, P. J. MURPHY, J. A. LANGTON, P. BARKER AND D. J. ROWBOTHAM

SUMMARY

We have studied the tone of the lower oesophageal sphincter (LOS) in 40 adults undergoing routine body surface surgery and allocated randomly to receive anaesthesia either by face mask and Guedel airway or by laryngeal mask airway. In the laryngeal mask group there was a mean (SEM) decrease in barrier pressure (LOS minus gastric pressure) of 3.6 (1.4) cm H_2O, compared with a mean increase of 2.2 (1.2) cm H_2O in the face mask group ($P < 0.005$).

KEY WORDS

Equipment: laryngeal mask, face mask. Gastrointestinal tract: lower oesophageal sphincter.

Regurgitation and aspiration of gastric contents have been reported in association with the use of the laryngeal mask airway (LMA) [1–6]. Previous work using dye studies has shown that the incidence of regurgitation of gastric contents may be increased during general anaesthesia with spontaneous ventilation using the LMA, compared with a group anaesthetized via a face mask and Guedel airway [7].

The major barrier to oesophageal regurgitation of gastric contents is accepted generally to be the lower oesophageal sphincter (LOS). This study was designed to investigate the effect of LMA insertion on LOS pressure during anaesthesia.

PATIENTS AND METHODS

Measurement of LOS pressure

LOS pressure was measured using a 3-mm diameter silastic orogastric probe containing subminiature strain-gauge pressure transducers (Gaeltec Ltd). These have advantages over larger diameter, water-perfused infusion manometers, causing less reflex activity and giving a more accurate reflection of the LOS pressure [8, 9]. The pressure signal was amplified and recorded onto a chart recorder (BTi Biox 2100).

At designated times during the study (see below), the probe was passed through the mouth into the stomach and a period of 15 min was allowed for reflex peristalsis caused by insertion of the probe to subside. The probe was then withdrawn through the lower oesophagus using a hand-withdrawn, slow-pull-through technique and a recording of the pressure was obtained. The barrier pressure was calculated as the difference between the intragastric pressure and the peak LOS pressure measured at the end of expiration. Such a technique has been shown to be reliable and not to miss significant pressure peaks [10].

Study design

After obtaining written informed consent and local Ethics Committee approval, we studied 40 patients (ASA I–II, aged 24–69 yr) undergoing body surface surgery. Patients were excluded if they were obese, taking drugs known to affect the LOS, or had a history of previous upper abdominal surgery, hiatus hernia, oesophageal reflux, peptic ulceration or diabetes mellitus.

All patients were unpremedicated. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and fentanyl 1 μg kg^{-1}, and maintained with 1.5% halothane and 67% nitrous oxide in oxygen, administered via a face mask and Guedel airway. Surgery was then allowed to commence. Ten minutes after induction of anaesthesia, the pressure probe was passed into the stomach. Fifteen minutes later, a baseline LOS pressure tracing was recorded using the technique described above. The probe was then re-introduced into the stomach.

Patients were allocated randomly, before anaesthesia, for subsequent maintenance with either face mask and Guedel airway or LMA after baseline measurements had been made. The patients in the LMA group had a lubricated LMA of appropriate size sited by an experienced anaesthetist in the manner described by Brain [11]. The cuff was inflated with an appropriate volume of air (size 3, 20 ml; size 4, 30 ml). Patients in the face mask and Guedal airway group continued under anaesthesia as before. Both groups continued to breathe a constant inspired concentration of 1.5% halothane and 66% nitrous oxide in oxygen. After 15 min, a second recording of LOS barrier pressure was made in both groups. No difficulty was experienced in with-

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TABLE I. *Patient characteristics (mean (range)). No significant differences between groups*

	Face mask group	LMA group
Number	20	20
Age (yr)	46.9 (25–69)	44.3 (24–68)
Sex (M:F)	11:9	11:9
Weight (kg)	71(51–86)	68(49–81)
Operation		
Inguinal herniorrhaphy	7	6
Varicose veins	8	6
Arthroscopy	5	8

TABLE II. *Effect of laryngeal mask insertion on lower oesophageal sphincter barrier pressure (mean (SEM)).* *$P < 0.05$; **$P < 0.01$ *compared with face mask group*

	LOS barrier pressure (cm H_2O)	
	Face mask group	LMA group
Baseline	18.0 (2.0)	17.7 (2.0)
Final	20.2 (2.5)	14.1 (1.7)*
Change	+2.2 (1.2)	−3.6 (1.4)**

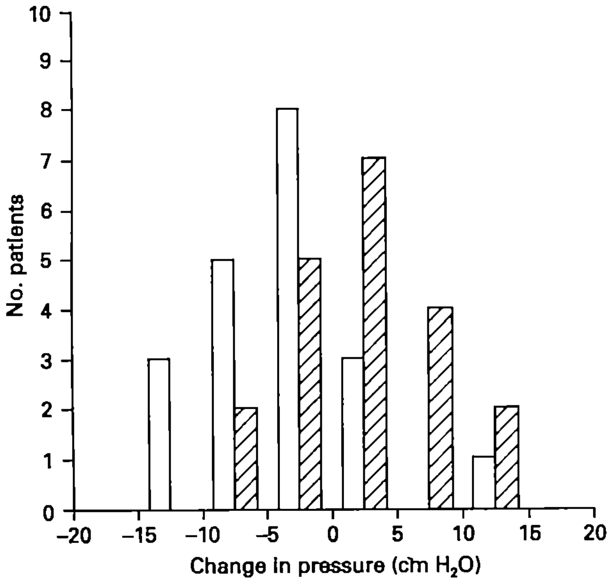

FIG. 1. Change in lower oesophageal barrier pressure during anaesthesia with face mask (▨) and laryngeal mask (☐).

drawing the LOS probe from behind the inflated LMA cuff, and no additional manipulation of the LMA was required.

All pressure recordings were coded, and interpreted by an independent blinded observer. The LOS barrier pressure for each tracing was calculated using the method described above.

Data were tested for normality using the Kolmogorov–Smirnov goodness of fit test, and analysed using Student's paired *t* test.

RESULTS

The groups were comparable in age, sex, weight and type of surgery (table I).

Two patients were withdrawn from the study because of difficulty in passing the oesophageal probe. There were no difficulties in inserting or placing the LMA.

There was no significant difference in baseline measurements of LOS barrier pressures between the groups (table II). There was a mean increase in barrier pressure of 15.4 (SEM 7.1)% in the face mask group, compared with a 15.8 (7.4)% reduction in the LMA group ($P < 0.005$) (table II).

LOS barrier pressure decreased considerably (by 10–15 cm H_2O) in three patients (fig. 1).

DISCUSSION

We have demonstrated that the LOS barrier pressure is reduced during general anaesthesia in some patients after insertion of an LMA when compared with a group anaesthetized via a face mask and Guedel airway.

The barrier pressure might have been affected by differences between the groups in the depth of anaesthesia. However, anaesthesia was standardized in each group and there were no differences in type of surgery. All patients had a clear airway throughout, and it is therefore unlikely that LMA insertion resulted in significant improvement of the airway such that the uptake of anaesthetic agent and depth of anaesthesia would be altered. Likewise, any differences caused by the effect of surgical stimulation would be expected to be the same in each group, as the numbers having each operation were similar, and all operations were performed by one of only two surgeons. The patients who demonstrated large decreases in LOS barrier pressure were not in any identifiable subgroup of patients.

Some of the drugs used in this study are known to decrease the LOS pressure, including thiopentone [12] and halothane [13]. No data for fentanyl are available, but other opioids are known to decrease the LOS pressure [9]. The effect of nitrous oxide on the LOS is less clear, as 67% nitrous oxide in oxygen has been reported to reduce the LOS pressure [13], but 50% has been reported not to affect it [14]. In any case, our study design ensured that there was no difference between the groups in exposure to any of these drugs.

We observed an increase in the LOS barrier pressure in the control face mask group during the study period. This may reflect a return towards pre-induction values as the plasma concentrations of drugs used to induce anaesthesia decreased as a result of redistribution and metabolism. This effect was presumably concealed in the LMA group patients by the reduction in LOS barrier pressure caused by the LMA.

No previous investigations have been made into the effect of the method of airway maintainance or of the LMA on the LOS barrier pressure. Therefore we cannot make any comparisons between our data and those of others. Other investigators have shown that normal individuals exhibit a large variation in LOS barrier pressures, and that there is considerable overlap in barrier pressures of normal subjects and those with reflux. A correlation exists between reflux and barrier pressure [15], and although it is not possible to define a barrier pressure below which reflux will occur, a reduction in barrier pressure would be expected to increase the risk of gastric reflux.

The mechanism of the observed reduction in LOS barrier pressure after LMA insertion is unknown. Events occurring proximally in the alimentary canal are known to have consequences distally. The presence of a bolus in the pharynx provokes a swallowing reflex in the awake human, and this is known to be associated with a marked but transient reduction in LOS pressure [16]. We did not observe any patient swallowing during this study, and the timing of measurements make it unlikely that this mechanism caused the reduction in LOS pressure. In contrast, sustained distension of the oesophagus by balloon induces prolonged relaxation of the LOS [17], and it may be that distension of the pharynx by the inflated LMA cuff similarly reduces the LOS barrier pressure.

In conclusion, this study has demonstrated that a decrease in LOS barrier pressure may occur when an LMA is used for airway management during anaesthesia with spontaneous ventilation. This may provide a possible explanation for the increased incidence of regurgitation of gastric contents that has been shown to occur when a LMA is used compared with a face mask [7]. Further work is necessary to establish the precise nature of this effect and its clinical significance.

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ANAESTHESIA FOR TRANSTHORACIC ENDOSCOPIC SYMPATHECTOMY IN THE TREATMENT OF UPPER LIMB HYPERHIDROSIS

R. JEDEIKIN, D. OLSFANGER, D. SHACHOR AND K. MANSOOR

SUMMARY

Renewed interest has been shown in transthoracic endoscopic sympathectomy (TES) for the treatment of upper limb hyperhidrosis. We review our experience and discuss the anaesthetic technique and perioperative problems encountered in 58 patients undergoing TES for hyperhidrosis. Patients were monitored for arterial pressure, heart rate, ECG, pulse oximetry (Sp_{O_2}), end-tidal carbon dioxide concentration, peak inspired airway pressure and skin temperature. General anaesthesia, with a double-lumen endobronchial tube, enabled the lungs to be collapsed alternately, thereby ensuring easy and clear access to the sympathetic chain. Controlled ventilation with 100% inspired oxygen was necessary to obviate hypoxaemia. In two patients, severe hypotension and bradycardia occurred during insufflation of carbon dioxide into the chest cavity. Four patients required underwater drainage of the pleural cavity for treatment of pneumothorax or haemothorax. The success and safety of the procedure depends on a scrupulous anaesthetic technique.

KEY WORDS

Anaesthesia: thoracic. Anaesthetic techniques: endobronchial. Surgery: transthoracic endoscopic sympathectomy.

Primary hyperhidrosis is a rare condition with an estimated incidence of 0.6–1.0% [1]. The aetiology is unknown. Excessive sweating usually affects the palms, axillae and feet; the face, groin and legs may be affected also [2–4]. It is often severely distressing, causing serious practical, psychological and social handicaps.

The treatment of palmar hyperhidrosis includes drugs, biofeedback, iontophoresis and percutaneous phenol block [4–7]. Sympathectomy is the most effective cure [4, 8–10] and may be performed simply and effectively by endoscopic transthoracic electrocautery [2, 3]. In 1978, Kux revived interest in this mode of treatment as an alternative to formal thoracotomy and surgical sympathectomy [11]. Transthoracic endoscopic sympathectomy (TES) provides the surgeon with a clear view of the anatomy of the internal chest wall and sympathetic chain. This improves the success of the procedure and decreases the incidence of complications such as Horner's syndrome and intercostal neuralgia. Additional advantages of TES are that it is minimally invasive, simple to perform, both sides may be undertaken under the same anaesthetic and the postoperative course is relatively benign, requiring only 12–24 h of hospital stay. Postoperative, radiologically diagnosed pneumothorax may occur, but rarely requires active treatment. Although the supraclavicular or axillary approaches to surgical sympathectomy have been advocated as improved alternatives to formal thoracotomy, their morbidity rate is significantly greater than that with TES [12].

On reviewing the literature, we could find no detailed description of the anaesthetic management of TES. We present here our initial anaesthetic experience with this procedure and discuss the perioperative management and complications.

PATIENTS AND METHODS

We studied prospectively 58 ASA I and II patients suffering from severe upper limb hyperhidrosis. There were 36 females and 22 males aged between 12 and 56 yr (mean age 25.4 yr).

A preoperative chest x-ray was taken in all patients. During the preoperative examination the patients were reassured and premedicated with a benzodiazepine (diazepam or midazolam).

During anaesthesia, the patients were monitored continually for arterial pressure, heart rate, ECG, and Sp_{O_2}. End-tidal carbon dioxide concentration and peak inspiratory pressures were monitored after tracheal intubation had been performed. Skin temperature was measured with thermistor probes attached to the index finger of each hand. An increase in temperature after cautery confirmed the success of the sympathectomy. Arterial blood-gas tensions were measured when deemed necessary.

Anaesthesia was induced with the patient in the supine position, with fentanyl 2 $\mu g\ kg^{-1}$ and thiopentone 3–5 $mg\ kg^{-1}$ followed by vecuronium

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0.7 mg kg^{-1}. After 2–3 min of mask ventilation with oxygen and an inhalation agent, with the patient deeply anaesthetized, a left-sided, double-lumen endobronchial tube (Carlens or left-sided Robertshaw) was inserted. Correct placement of the endobronchial tube was confirmed in the standard way by observation and auscultation. In 25 patients intubation was facilitated using an intubating fibreoptic laryngoscope as advocated by Benumof [13].

Anaesthesia was maintained with isoflurane or halothane and increments of fentanyl and vecuronium as required. The lungs of all patients were ventilated with 100 % oxygen throughout the procedure. A tidal volume of 10–12 ml kg^{-1} was used to ventilate both lungs. It was reduced to 8–6 ml kg^{-1} during one-lung ventilation, thereby avoiding excessively great peak inspiratory pressures. During the procedure, the patient was positioned in a 20° anti-Trendelenberg position, with both arms abducted to 90°.

Before insertion of the endoscope into the pleural cavity, the ipsilateral lung was partially collapsed by disconnecting the endobronchial tube from the ventilator and opening it to air. The lung was compressed further by insufflating carbon dioxide 0.5–1.5 litre via a Verrez needle inserted into the pleural space through a small skin incision in the fourth intercostal space, mid-axillary line. The patient was monitored closely and observed during this period. Then, after the removal of the Verrez needle, the endoscope was inserted through the same skin incision and the sympathectomy performed by electrocautery of the sympathetic chain. After completion of the procedure, the endobronchial tube was reconnected and the lung manually reinflated under direct vision. The endoscope was removed when the reinflated lung was seen to bulge into it and controlled bilateral ventilation resumed. In 43 patients, the procedure was then repeated on the other side. In the recovery room close attention was paid to haemodynamic, pulse oximetric monitoring and pain relief. A chest radiograph was taken 30–60 min after admission of the patient to the recovery room, to check for full lung expansion.

RESULTS

One hundred and one sympathectomies were performed in 58 patients. Forty-three patients underwent bilateral and 15 unilateral TES. Operating time for bilateral sympathectomy was from 20 to 75 min. Arterial pressure and heart rate remained stable during operation in 56 of the 58 patients. In two patients, while carbon dioxide was insufflated through the Verrez needle, a sudden bradycardia of less than 40 beat min^{-1} occurred, associated with a decrease in arterial pressure to less than 50 mm Hg systolic and Sp_{O_2} to 70 %. This was relieved by the immediate removal of carbon dioxide from the chest cavity.

The Sp_{O_2} was in the range 99–100 % in 32 patients, 95–98 % in 21 patients and 88–95 % in three patients.

Unilateral pneumothorax, diagnosed in eight patients, resolved spontaneously in six and required underwater drainage in two. Subcutaneous emphysema was seen in two patients. Haemothorax needing drainage was diagnosed with the aid of postoperative chest x-rays in two patients.

Fifty-six patients complained of postoperative chest pain. The pain was mainly retrosternal and most distressing during the first 2–4 h after surgery. Except for the four patients who developed a pneumothorax or haemothorax, needing underwater drainage, all patients were discharged from hospital within 24 h of surgery.

Two patients developed a temporary Horner's syndrome, lasting 1 week in one patient and 3 months in the other.

DISCUSSION

Total collapse of the lung for this procedure enables complete vision of the upper sympathetic chain and decreases the risk of surgical trauma to the lung, stellate ganglion and neighbouring blood vessels. Endobronchial anaesthesia allows the appropriate lung to be collapsed under full control and both sides to be operated on in one session. We found the Carlen or left-sided Robertshaw tube to be adequate. Confirmation of correct tube positioning with auscultation was sufficient in most patients. However, the fibreoptic laryngoscope was a useful adjunct in the occasional problematic subject. Before the Verrez needle is inserted, the ipsilateral side of the double-lumen tube should be disconnected from the ventilator and opened to air. This causes the lung to fall away from the chest wall, reducing the danger of puncturing the lung with the Verrez needle. Incorrect placement of the double-lumen endobronchial tube increases the risk of this complication.

The sudden haemodynamic instability which occurred in two patients was caused probably by rapid and excessive insufflation of carbon dioxide into the closed chest cavity, which displaced the mediastinum, compressed the lungs and large veins and decreased venous return to the heart. This was relieved immediately by removal of carbon dioxide from the chest. The surgeon should be aware of this complication and desist from too rapid insufflation of carbon dioxide. We found that insufflation of carbon dioxide up to 1 litre is sufficient to collapse the lung.

The avoidance of systemic hypoxia is another important problem to be addressed. The use of pulse oximetry is mandatory. Forty-five percent of our patients had an Sp_{O_2} less than 98 %. The normal pulmonary vascular response to atelectasis of the lung is an increase in pulmonary vascular resistance. This protective mechanism, whereby pulmonary blood flow is diverted from the atelectatic to the ventilated lung, appears to be most effective when 30–70 % of the lung is hypoxic [14]. It may well be that, by the insufflation of carbon dioxide into the closed chest cavity, the amount of collapsed lung that becomes hypoxic is in excess of 70 %, causing the protective effect of hypoxic pulmonary vasoconstriction to be abolished and the Pa_{O_2} to decrease. This would explain the small Sp_{O_2} seen in 24 of the 58 patients. We suggest, therefore, that it is imperative that all patients receive 100 % oxygen during TES.

In only eight of the 101 sympathectomies performed was a postoperative pneumothorax diagnosed on chest x-ray. These results are similar to those found in recent studies in which TES was used [2, 3, 12]. In six of our patients the pneumothorax was small, symptomless and probably the result of incomplete expulsion of carbon dioxide from the chest cavity at the end of the procedure. Active intervention was not required, and by the second day after operation the chest x-ray was normal. These pneumothoraces can be prevented by reinflating the lungs under direct vision until they are seen to bulge into the lumen of the endoscope. The endoscope is then removed and the hyperinflation ceased, as it may cause subcutaneous emphysema. A control postoperative chest x-ray is necessary. Chest drains were inserted in two of our patients when, after 48 h, the pneumothorax showed no signs of resolving. The probable cause of the pneumothorax in these patients was accidental trauma to the lung by the cautery.

Postoperative pain was observed in nearly all our patients and was most severe in the first 2–4 h after surgery. It was usually retrosternal, but also presented as upper back pain and was relieved by opioids.

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PERIOPERATIVE CONTINUOUS MONITORING OF ST-SEGMENT CHANGES IN PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION

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SUMMARY

Using continuous ambulatory electrocardiography, we have investigated the incidence of ST-segment changes occurring in patients undergoing elective Caesarean section under extradural, spinal or general anaesthesia. There was no evidence of significant perioperative ST-segment changes. The findings contrast with the results of other work published recently.

KEY WORDS

Anaesthesia: obstetric, Caesarean section. Anaesthetic techniques: extradural, spinal. Heart: myocardial ischaemia.

A high incidence of electrocardiographic changes during Caesarean section under regional anaesthesia has been reported [1]. This study found also a statistically significant correlation between symptoms of chest pain, pressure or dyspnoea and ECG changes during surgery. If the cause of these changes were myocardial ischaemia, this would have important implications for the anaesthetic management of patients undergoing Caesarean section. However, this study did not include preoperative ECG assessment, monitoring of perioperative ECG changes was intermittent and there was no control group receiving general anaesthesia. Therefore, we have investigated the incidence of ST-segment abnormalities during Caesarean section under regional and general anaesthesia using a computerized ambulatory ECG surveillance system.

PATIENTS AND METHODS

We studied 29 patients (ASA I) undergoing elective Caesarean section. The study was approved by the local Ethics Committee and patients gave informed, written consent. Patients with essential hypertension, pregnancy-induced hypertension or diabetes mellitus were excluded. Extradural, spinal or general anaesthesia was performed according to the preference of the patient after discussion with the anaesthetist.

Anaesthetic technique

Ranitidine 150 mg was administered orally the night before, and on the morning of, surgery. In addition, 0.3-mol litre^{-1} sodium citrate 30 ml was given 15 min before anaesthesia. All patients were transported to the operating theatre in the left lateral position and 15° left lateral tilt was maintained on the operating table until delivery of the infant.

Patients receiving extradural anaesthesia were given Ringer's lactate solution 1 litre and an extradural catheter was inserted in the 2nd or 3rd lumbar intervertebral space via a 16-gauge Tuohy needle. A test dose of 2% lignocaine 3 ml was administered, followed by two 10-ml aliquots of 2% lignocaine with 1:200000 adrenaline.

Patients receiving spinal anaesthesia were given Ringer's lactate solution 1 litre and Haemaccel 500 ml. A 26- or 27-gauge spinal needle was inserted in the 3rd lumbar interspace with the patient in the sitting position. Hyperbaric 0.5% bupivacaine 2.5 ml was injected, and the patient placed in the supine position with 15° left lateral tilt. In addition, ephedrine 6 mg i.v. was given on injection of bupivacaine.

All patients receiving regional anaesthesia had sensory anaesthesia to at least the T6 dermatomal level before surgery commenced. Arterial pressure was measured non-invasively every 3 min (Cardiocap, Datex). Ephedrine 3 mg was administered i.v. as required to maintain systolic arterial pressure greater than 90–100 mm Hg. Oxygen was given continuously via a Hudson mask (4 litre min^{-1}) until delivery and then discontinued. All patients received oxytocin 10 i.u. after delivery. Extradural catheters were removed at the end of the operation.

Patients receiving general anaesthesia were not given i.v. fluids before induction of anaesthesia. After preoxygenation for 3 min, anaesthesia was induced with thiopentone 5 mg kg^{-1} followed by suxamethonium 1.5 mg kg^{-1} to facilitate tracheal intubation. Cricoid pressure was applied from the start of the induction sequence until tracheal intubation was completed successfully. Anaesthesia was maintained with 1% enflurane and 50% nitrous oxide in oxygen and atracurium 0.5 mg kg^{-1}. The lungs were ventilated to normocapnia (Cardiocap, Datex). After delivery of the infant, papaveretum

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TABLE I. *Patient age, heart rate and mean arterial pressure (MAP) (mean (range)) before surgery. No significant differences between groups*

Group	Age (yr)	Heart rate (beat min^{-1})	MAP (mm Hg)
General ($n = 10$)	30.8 (22–42)	75 (60–105)	102 (86–121)
Extradural ($n = 11$)	29.3 (22–34)	80 (65–100)	100 (78–123)
Spinal ($n = 8$)	31.3 (26–39)	82 (71–90)	94 (86–113)

TABLE II. *Median (range) duration of patient monitoring with Compas monitor (min)*

Group	Time (min)		
	Preoperative	Peroperative	Postoperative
General ($n = 10$)	150 (135–300)	45 (35–60)	90 (60–105)
Extradural ($n = 11$)	135 (60–1020)	35 (21–50)	120 (60–360)
Spinal ($n = 8$)	214 (45–264)	54 (35–90)	116 (40–213)

0.3 mg kg^{-1} was administered i.v. and nitrous oxide increased to 66%. Residual neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg.

ECG and haemoglobin oxygen saturation (Cardiocap, Datex) were recorded in all patients during surgery.

Postoperative analgesia was provided in all groups by papaveretum 0.3 mg kg^{-1} i.m., given by the nursing staff at the request of the patient.

ECG monitoring

Continuous ambulatory ECG monitoring was used to record ECG abnormalities during the perioperative period using the Compas computerized ambulatory ECG surveillance system (Cardiac Care Units Inc.). The units are programmed to detect, record and analyse ECG abnormalities using three standard leads (V2, V5 and AVF). In particular, ST-segment changes lasting more than 30 s and the time of these events are recorded. Stored data are transferred to a dedicated printer and a report generated. The computer printout includes a baseline ECG, numerical and graphical recordings of ST-segment changes, atypical beats and arrhythmias. ST-segment depression of 1 mm or greater and ST elevation of 2 mm or greater for a minimum of 1 min were considered significant in this study.

A patient marker button allows the precise time of significant events to be recorded and this was used to record the times of induction of anaesthesia, use of ephedrine, delivery of the infant, patient discomfort and end of surgery. This enabled correlation between ECG abnormalities and specific events.

During surgery, any spontaneous complaints by patients receiving extradural or spinal anaesthesia were recorded. After surgery, patients were asked directly if they suffered any pain or about discomfort in any part of the body during the procedure.

Data were analysed using analysis of variance and chi-square test as appropriate.

RESULTS

The groups were similar in age, preoperative arterial pressure and heart rate (table I).

There were no significant differences in perioperative changes in heart rate and mean arterial pressure in each group (figs 1, 2).

Median (range) duration of Compas monitoring is shown in table II and the total cumulative duration of Compas monitoring and duration of ST-segment changes in table III. Three episodes of ST-segment depression were detected during the study. One patient in the general anaesthesia group experienced 1 min of ST depression 2 h before surgery. The second episode was of 6 min duration and occurred in the extradural group, 5 min before the i.v. infusion was commenced. A single 1-min episode of ST-

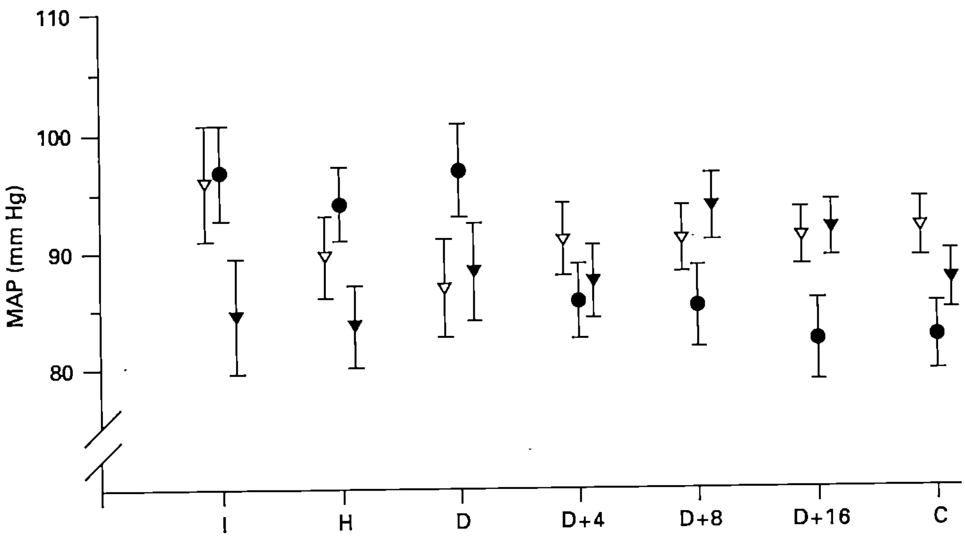

FIG. 1. Mean arterial pressure (MAP) (mean (SEM)). I = Incision; H = hysterotomy; D = delivery; D+4, D+8, D+16 = times (min) after delivery; C = closure. ● = General anaesthesia; ▽ = extradural; ▼ = spinal anaesthesia.

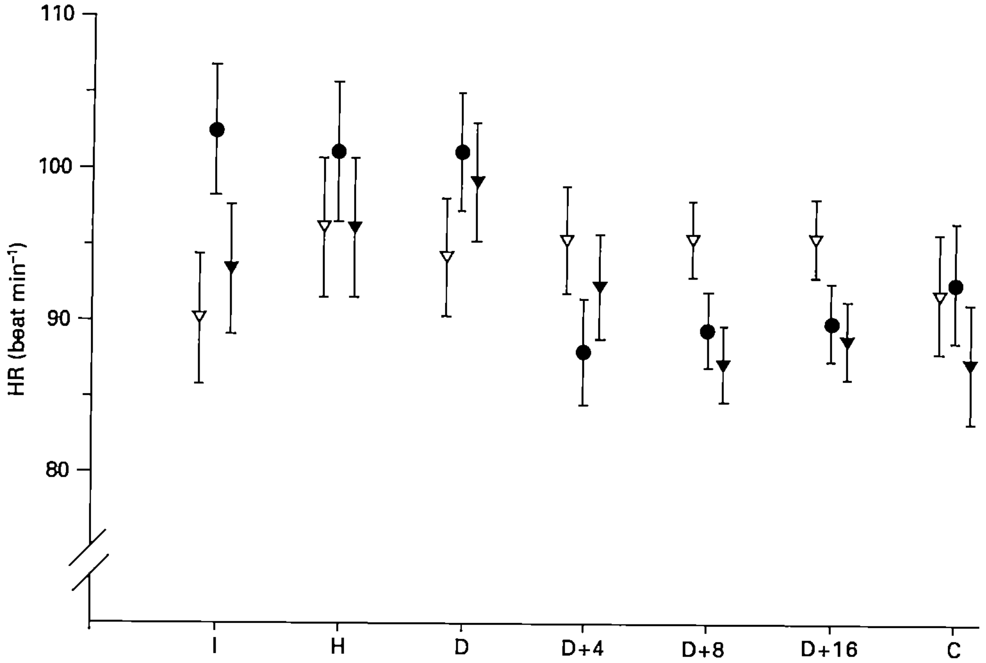

FIG. 2. Heart rate (HR) (mean (SEM)). I = Incision; H = hysterotomy; D = delivery; D+4, D+8, D+16 = times (min) after delivery; C = closure. ● = General anaesthesia; ▽ = extradural; ▼ = spinal anaesthesia.

TABLE III. *Cumulative duration of ST-segment monitoring and ST-segment changes*

Group	Period	Cumulative time (min)	ST-segment changes (min)
General	Preop.	1860	1
($n = 10$)	Perop.	430	0
	Postop.	1455	0
Extradural	Preop.	2400	6
($n = 11$)	Perop.	357	0
	Postop.	1455	0
Spinal	Preop.	1594	0
($n = 8$)	Perop.	490	0
	Postop.	1000	1

segment depression occurred in a patient in the spinal group 2 h after surgery. No symptoms were associated with any of these episodes.

No ST-segment changes were detected during surgery. One patient in the extradural group complained of chest pain and another in the spinal group of a feeling of heaviness on the chest. These symptoms were not associated with ST-segment changes.

There were no episodes of ST segment elevation in any patient during the study.

DISCUSSION

We have found no significant evidence of perioperative ST-segment changes suggestive of myocardial ischaemia in healthy patients undergoing Caesarean delivery under general or regional anaesthesia. One patient in the extradural group reported symptoms of chest discomfort and another in the spinal group described a feeling of heaviness on the chest, but these symptoms were not associated with ST-segment changes. Three brief and probably insignificant periods of ST-segment change were recorded, one episode in each of the three patient groups, two occurring before and one after surgery. It is not likely that these brief episodes represented myocardial ischaemia.

A much greater incidence of ECG changes occurring during Caesarean section under regional anaesthesia has been reported by Palmer and colleagues [1]. ECG changes described as compatible with myocardial ischaemia were recorded in 44 of 93 patients (47.3%) and in 35 of these (37.6%) the changes were considered to be characteristic of myocardial ischaemia. Furthermore, 15 patients reported symptoms of chest pain, pressure or dyspnoea and, in every case, these symptoms were associated with ECG changes. These findings are remarkable and the present study has reached significantly different conclusions. If, as suggested by Palmer and colleagues, the incidence of myocardial ischaemia in this group of patients is 37.6%, the power of our study is high, despite the relatively small number of patients. Under these circumstances, the likelihood of not detecting changes consecutively in 19 patients under regional anaesthesia is extremely small.

Differences in methodology between the two studies might have led to these discrepancies. In the present study, three standard anaesthetic techniques were used, whereas in the earlier study, a variety of agents were used in the extradural group and 0.75% bupivacaine in the spinal group. In the latter study, all patients achieved a level of sensory anaesthesia to at least T4, whereas the minimum level in this study was T6. A higher level of sensory anaesthesia would be more likely to block the cardiac sympathetic innervation, affecting myocardial performance deleteriously.

Sudden hypervolaemia in the presence of sympathetic block increases myocardial work and oxygen requirements [2]. Different volumes of fluid were used before surgery in the two studies: in our study, the extradural group received 1 litre and the spinal group 1.5 litre; in the earlier study, all patients received 2 litre i.v. The effect of uterine autotransfusion at delivery, combined with prehydration, could lead to excessive demands on the myocardium and cause ST-segment changes. However, this would be more likely to occur with the use of larger volumes and it is difficult to envisage how a difference of 0.5–1.0 litre would have such a profoundly greater effect on myocardial work and oxygen requirements, causing widespread ST-segment changes.

The Compas continuous ambulatory ECG monitoring system was used in our study. This has been found to be a sensitive system for the detection of ST-segment changes in the perioperative period [3, 4]. Our definition of significant ST-segment changes, which is that accepted generally, was a depression of 1 mm or greater and elevation of 2 mm or greater that lasted longer than 1 min. The ST-segment changes detected in the earlier study were from intermittent ECG recordings and these might detect ST-segment changes of very short and insignificant duration. It is probable that the different methods used to record ECG were a major factor in the incongruous findings.

There are several factors in addition to myocardial ischaemia that may cause ST segment changes, including ventricular hypertrophy, electrolyte imbalance, drugs and conduction disturbances. However, it is most unlikely that any of these factors was present to a significant extent in the two studies.

In the present study, only two of 29 patients complained of chest symptoms and these were not associated with ST-segment changes. A high incidence of chest discomfort was described by Palmer and colleagues in association with ST-segment changes [1]. Malinow and others have described similar symptoms associated with ultrasonic evidence of venous air emboli during Caesarean section under regional anaesthesia [5]. In this last study, chest pain was reported in 24 of the 46 women with Doppler change, whereas only two of the 43 women without Doppler change reported chest pain. These changes were also associated with dyspnoea in nine of 46 women. ECG changes were not reported in this study. The overall incidence of chest pain (26/89) was again much greater than in our study. The two episodes of chest pain in our study occurred during surgery and may have been related to venous air emboli, but were not associated with ST-segment changes.

In conclusion, we have found no ECG evidence of significant intraoperative myocardial ischaemia in patients undergoing Caesarean section under either regional or general anaesthesia. Further investigation is required to explain the major differences between the findings of this study and the work of Palmer and colleagues, but we believe that significant myocardial ischaemia is very infrequent in healthy patients undergoing elective Caesarean section.

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EEG BURST SUPPRESSION WITH PROPOFOL DURING CARDIOPULMONARY BYPASS IN CHILDREN: A STUDY OF THE HAEMODYNAMIC, METABOLIC AND ENDOCRINE EFFECTS

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SUMMARY

We have studied the effects of propofol, given to maintain EEG suppression throughout cardiopulmonary bypass (CPB), in 20 children aged 1–15 yr, in a parallel group comparison. Anaesthesia was produced by fentanyl 50 μg kg⁻¹, enflurane or halothane and midazolam 0.1 mg kg⁻¹ at the start of CPB. After randomization, 50 % of the children also received propofol during CPB. All children were cooled during CPB (25–28 °C) and pump flows (non-pulsatile) were 2.4 litre min⁻¹ m⁻², reducing to 1.2–1.6 litre min⁻¹ m⁻² during hypothermia. Large rates of infusion of propofol were required to maintain EEG suppression, particularly during rewarming. Compared with control, the propofol group showed significant increases in mixed venous oxygen saturation and significant reductions in systemic oxygen uptake and glucose and cortisol concentrations. There were no differences in triiodothyronine and lactate concentrations, mean arterial pressure during CPB and inotrope requirement after CPB, or in recovery times.

KEY WORDS

Anaesthetics, intravenous: propofol.

Cardiopulmonary bypass (CPB) may be associated with multi-organ damage, resulting in both immediate and long-term effects [1, 2]. This damage may be related in part to inadequate regional tissue oxygen delivery, and also to the well documented "stress response" during and after CPB [3]. Reduction in the stress response to non-cardiac surgery in children is associated with improved postoperative outcome [4, 5]. Damage caused by inadequate oxygen delivery and tissue hypoxia may be reduced by metabolic depression using both hypothermia and anaesthetic agents. These effects may be additive; for example, cerebral metabolic depression, in addition to that caused by hypothermia, may be produced with thiopentone or isoflurane titrated to EEG suppression during CPB [6]. With thiopentone, this may result in reduced cerebral damage; however, because of its side effects in the large doses required for EEG suppression, it may not be the most suitable agent for organ protection [7].

Propofol has a short half-life and, when given by infusion, has been shown to suppress the EEG [8] and reduce whole body oxygen uptake ($\dot{V}O_2$) during hypothermic CPB (28 °C) in adults [9]. Propofol has also been shown to suppress seizures [10, 11] and may act as an oxygen free radical scavenger [12]. These properties are of potential benefit in organ protection [13]. In animal models, propofol also improved recovery after cerebral ischaemia [14, 15]. The aim of this study was to examine the effect of propofol, given to produce EEG suppression during CPB, on the haemodynamic, metabolic and endocrine responses in children.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and informed consent was obtained from the parents of 20 children undergoing elective open heart surgery. As experience with propofol for paediatric cardiac anaesthesia is limited, children with complex cyanotic abnormalities, congestive cardiac failure, significant pulmonary vascular disease and age < 1 yr were excluded.

Patients were premedicated with trimeprazine 2–3 mg kg⁻¹ (maximum dose 90 mg) or, for the older children, temazepam 0.3 mg kg⁻¹ approximately 1.5 h before surgery. Anaesthesia was induced with ketamine 2 mg kg⁻¹, fentanyl 10–20 μg kg⁻¹ and pancuronium 0.1 mg kg⁻¹. The trachea was intubated and the lungs ventilated with 50 % nitrous oxide in oxygen before CPB and 100 % oxygen after CPB. All patients received a total of 50 μg kg⁻¹ of fentanyl by the start of CPB, supplemented as required with halothane or enflurane. Monitoring included ECG, pulse oximetry, direct arterial pressure, central venous pressure, oesophageal and rectal temperature, urine output and continuous EEG using a cerebral function analysis monitor (CFAM).

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Phenoxybenzamine 0.5–1 mg kg^{-1} was given at the discretion of the anaesthetist before CPB, to assist in even cooling and rewarming. No other vasoactive drugs were administered before the termination of CPB, when dopamine was given, again at the discretion of the anaesthetist. Maintenance fluids before and after CPB comprised 0.45% sodium chloride in 5% glucose, supplemented with plasma protein solution, fresh frozen plasma and concentrated red cells as required.

A standard CPB technique was used in all patients. Before cannulation, patients were anticoagulated with heparin 3 mg kg^{-1}. The bypass circuit consisted of a membrane oxygenator (COBE), a roller pump (Stockert Instruments) and an arterial filter (Bentley) primed with lactated Ringer's solution and concentrated red cells to achieve a PCV of 25%. Priming volumes varied from 1 to 2 litre, depending on patient size. Methylprednisolone 10 mg kg^{-1} was added to the pump prime. Other additions to the pump prime included heparin, mannitol, potassium chloride, sodium bicarbonate and cefotaxime in appropriate doses. During CPB, moderate hypothermia (25–28 °C), non-pulsatile perfusion and pH management (addition of carbon dioxide to pump gases, aiming to maintain a temperature-corrected arterial pH of 7.40) were used. Pump flows were 2.4 litre min^{-1} m^{-2}, reducing to 1.2–1.6 litre min^{-1} m^{-2} during stable hypothermia. Cardioplegia consisted of 20–30 ml kg^{-1} of St Thomas's solution (1 litre of Ringer's solution, with added potassium, magnesium and procaine). At the onset of CPB, all patients had received a total of fentanyl 50 µg kg^{-1} and, in addition, midazolam 0.1 mg kg^{-1} and pancuronium as CPB commenced.

After random allocation to groups, 10 children did not receive further anaesthetic supplements during CPB (control group). The other 10 children (propofol group) received a bolus of propofol 3 mg kg^{-1} at the start of CPB, followed by an infusion titrated to maintain EEG burst suppression throughout CPB. A further bolus of propofol 1.5 mg kg^{-1} was given at the start of rewarming. Propofol was infused directly into the venous reservoir of the oxygenator. After CPB, anticoagulation was reversed with protamine.

Mean arterial pressure, oesophageal temperature, pump flow rate and propofol infusion rates were noted at specific stages during CPB. Blood samples were aspirated from the venous and arterial ports of the oxygenator 5 min after stable hypothermia was achieved and at normothermia immediately before termination of CPB. These samples were placed in ice and then analysed for Po_2, Pco_2 and pH (Corning 178 blood-gas analyser) and for haemoglobin and oxygen saturation (IL 282 Co-oximeter). Oxygen content, oxygen delivery (Do_2) and oxygen uptake ($\dot{V}o_2$) were calculated. Additional samples of venous blood at these times were placed in heparinized bottles for subsequent measurement of propofol concentration by high pressure liquid chromatography. Venous blood was also sampled after induction (PI), at the start of CPB (SB), the end of CPB (EB), and 3 and 24 h after CPB for measurement of PCV and plasma concentrations of total protein, albumin, glucose, lactate, cortisol and triiodothyronine (T3). Measured values of cortisol and T3 at SB, EB and 3 h post-bypass were corrected for haemodilution using albumin concentrations as follows:

Corrected value =

$$\text{measured value} \times \frac{\text{initial (post-induction) albumin concn}}{\text{new albumin concn}}$$

Details of mean arterial pressure, core temperature, peripheral temperature, urine output and use of inotropes were recorded on arrival of the patient in the intensive care unit (ICU) and for the first 6 h thereafter. Arterial blood-gas tensions on arrival in the ICU, the times to awakening, first analgesia, tracheal extubation and discharge from the unit and postoperative complications were noted.

Data were analysed using Student's *t* test, analysis of variance (ANOVA) for repeated measures, Mann–Whitney *U* and Wilcoxon tests as appropriate. A significance level of 5% was assumed.

RESULTS

There were no significant differences between the two groups in age, weight, surface area, duration of CPB or type of surgery (tables I, II). Table III shows the propofol infusion rates and resultant venous concentrations of propofol required to maintain EEG burst suppression at various stages during CPB. Examples of typical CFAM tracings in the two groups are shown in figure 1.

Phenoxybenzamine was given to seven patients in each group. There were no significant differences in mean arterial pressure between the two groups during the various stages of CPB. Patients who did not receive phenoxybenzamine had greater mean arterial pressure when "warm" in the propofol group ($P < 0.05$). However, these were small numbers in these subgroups and differences in their mean ages (control group 2.7 yr; propofol group 10.5

TABLE I. *Patient characteristics and duration of cardiopulmonary bypass (mean (range or* SD*))*

	Control group	Propofol group
Sex (M/F)	6/4	3/7
Age (yr)	5.9 (2–14)	6.4 (1–15)
Weight (kg)	22.3 (14.8)	23.8 (21.3)
Surface area (m^2)	0.84 (0.4)	0.82 (0.5)
Cardiopulmonary bypass (min)	50.8 (20.6)	48.6 (11.6)

TABLE II. *Details of type of surgery performed (No. per group). ASD = Atrial septal defect; PS = pulmonary stenosis; PA = pulmonary artery; PAPVD = partial anomalous pulmonary venous drainage*

	Control group	Propofol group
ASD	4	4
ASD + other (e.g. PS)	3	2
Aortic stenosis	2	2
Deband + patch PA	1	—
Mitral stenosis	—	1
PAPVD	—	1

TABLE III. *Propofol infusion rates and resultant propofol concentrations to maintain EEG burst suppression during cardiopulmonary bypass in children (mean (SD)).* *$P < 0.05$; **$P < 0.001$ *(comparison between successive stages by ANOVA)*

	Cooling	Cold	Rewarming	Warm
Infusion rate (mg kg^{-1} h^{-1})	17 (4.9)	13 (5.5)*	26 (7.9)**	30 (8.4)*
Venous propofol concn (μg ml^{-1})		3.75 (1.2)		8.44 (2.7)**

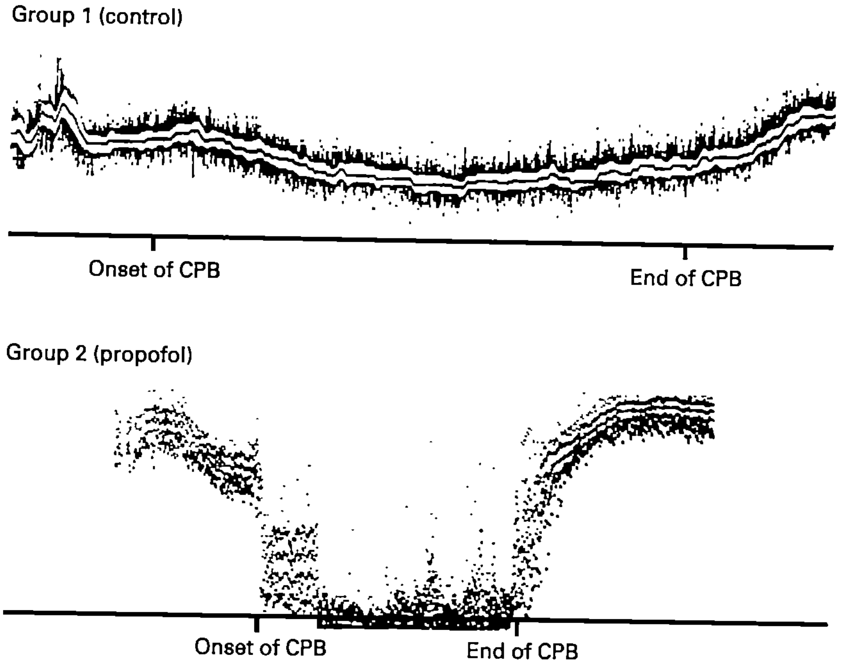

FIG. 1. Cerebral function analysis monitor recordings during bypass, from a single control patient and from a single patient who received propofol.

TABLE IV. *Oesophageal temperature, haemoglobin concentration (Hb), mixed venous oxygen saturation* ($S\bar{v}_{O_2}$)*, systemic oxygen delivery* (D_{O_2}) *and systemic oxygen uptake* ($\dot{V}_{O_2}$) *during cardiopulmonary bypass (mean (SD)).* *$P < 0.05$; **$P < 0.01$ *(between groups)*

	Hypothermia		Normothermia	
	Control	Propofol	Control	Propofol
Temp. (°C)	27.9 (1.68)	26.5 (1.32)	36.8 (0.37)	36.4 (0.84)
Hb (g dl^{-1})	7.2 (1.74)	7.9 (1.48)	7.9 (1.59)	8.5 (1.00)
$S\bar{v}_{O_2}$ (%)	73 (10)	86 (6)**	60 (9.1)	73 (6.8)**
D_{O_2} (ml min^{-1} m^{-2})	157 (39)	181 (63)	266 (52)	287 (39)
$\dot{V}_{O_2}$ (ml min^{-1} m^{-2})	45 (22)	28 (13)	101 (26)	82 (13)*

yr). Five children in the control group and six children in the propofol group received dopamine 5–10 μg kg^{-1} min^{-1} when CPB was terminated. One child in the propofol group (partial anomalous pulmonary venous drainage repair) also required a bolus of isoprenaline after a long bypass and with ST-segment changes thought to be related to air in the coronary arteries. Otherwise, no other inotropes were used in the period after bypass.

Details of mixed venous saturation ($S\bar{v}_{O_2}$) oxygen delivery (D_{O_2}) and oxygen uptake ($\dot{V}_{O_2}$) at hypothermia and normothermia during CPB are shown in table IV. D_{O_2} values were greater in the propofol group at both temperatures, mainly as a result of greater haemoglobin concentrations. Pump flow rates were also slightly greater at hypothermia in the propofol group: 1.6 (SD 0.33) litre min^{-1} m^{-2} compared with 1.56 (0.2) litre min^{-1} m^{-2} in the control group (ns). Despite this, $S\bar{v}_{O_2}$ values were significantly greater in the propofol group at both temperatures ($P < 0.01$). $\dot{V}_{O_2}$ values were smaller in the propofol group at both temperatures, this being statistically significant at normothermia ($P < 0.05$).

Plasma concentrations of albumin decreased in both groups at the start of CPB, from mean values of 40 g $litre^{-1}$ (PI) to 18 g $litre^{-1}$ (SB), remained decreased during CPB and increased to about 35 g $litre^{-1}$ (3 h) after CPB. Changes in glucose, cortisol, T3 and lactate concentrations are shown in figure 2. The propofol group had smaller concentrations of glucose compared with the control group, this being statistically significant at the end of CPB ($P < 0.05$).

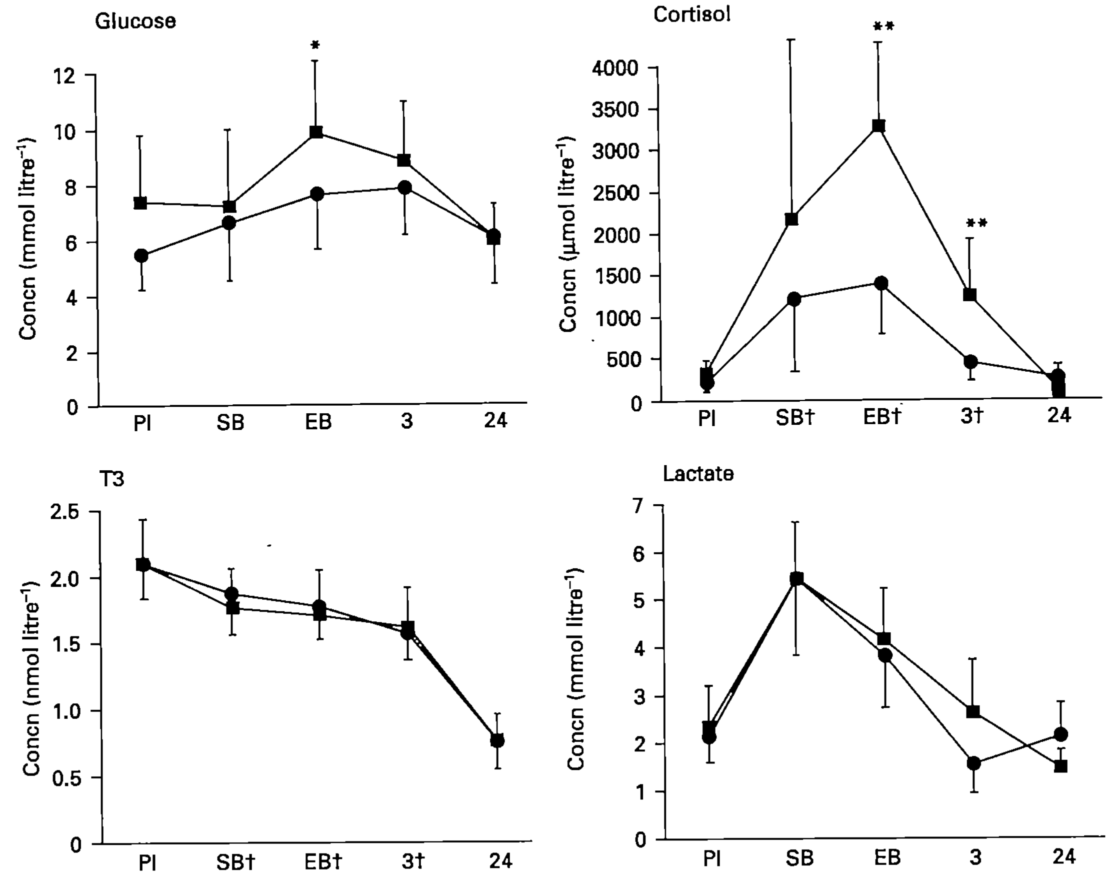

FIG. 2. Changes in concentrations of glucose, cortisol, T3 and lactate before, during and after bypass in children (mean, SD). PI = After induction; SB = at the start of CPB; EB = at the end of CPB; 3, 24 = 3 h and 24 h after CPB (for hormone measurements). ■ = Group 1 (control); ● = group 2 (propofol). $*P < 0.05$; $**P < 0.01$; † Corrected for haemodilution.

After correction for haemodilution, cortisol concentrations increased to very large values during and 3 h after CPB in the control group. By comparison, in the propofol group cortisol concentrations were 44 % smaller after the start of CPB, 58 % smaller at the end of CPB ($P < 0.01$) and 66 % smaller 3 h after bypass ($P < 0.01$). By 24 h, cortisol concentrations in both groups were similar to PI values. These changes contrast with those for T3, which showed significant decreases in both groups during and after CPB. By 24 h, T3 concentrations were only about 35 % of PI values, with no difference between the groups. The mean lactate concentrations in the pump prime after circulation but before the start of CPB were 11.0 mmol litre^{-1} in both groups. Blood concentrations of lactate increased at the start of CPB, decreased during CPB and decreased again to near PI values by 3 h after bypass in both groups.

Detailed analysis of the recordings during the first 6 h in the intensive care unit (ICU) showed no significant difference between the two groups in mean arterial pressure, peripheral temperature, core–peripheral temperature gradient, urine output, oxygen requirements ($F_{I_{O_2}}$), or in pH and base excess on arrival in the ICU. Both groups had a mean peripheral temperature greater than 36.0 °C by 4 h.

TABLE V. *Recovery times from skin closure (mean (SD)). No significant differences between groups*

	Recovery time (h)	
	Control group	Propofol group
Awakening	2.0 (1.39)	2.54 (1.1)
First analgesia	2.05 (1.38)	2.97 (1.58)
Extubation	9.9 (5.9)	7.5 (2.66)
Discharge from ICU	24.5 (1.8)	25.7 (1.5)

Two children in the control group had hypotensive episodes and one child had a right upper lobe collapse; otherwise, recovery was uneventful in both groups. In the propofol group, times to awakening and first analgesic requirement were longer than in the control group, but the time to tracheal extubation was shorter (ns). Both groups had similar discharge times from the ICU (table V).

DISCUSSION

Prevention of organ damage associated with cardiopulmonary bypass remains one of the goals of the cardiac anaesthetist. Cerebral damage has been well documented in both adults [1] and children [16]. Significant damage to other organs may occur also, including the lungs and kidneys [2]. The major causes of this damage are inadequate perfusion and micro- and macroembolism [21], which are most likely to occur at the start of CPB, after aortic declamping and at the end of CPB.

"Hypothermia" is the most effective method of providing cerebral protection during CPB [1]. As the body temperature is reduced, a progressive reduction in cerebral metabolic requirement for oxygen ($CMRo_2$) enhances the brain's tolerance to ischaemia. Deep hypothermia alone (temperatures less than 20 °C) produces EEG suppression and is used routinely for total circulatory arrest in neonates, with relative safety [18]. Disadvantages include longer bypass times and increased peripheral vasoconstriction. For routine surgery, most cardiac centres use moderate hypothermia (25–32 °C) with low flow CPB to provide cerebral protection. Unfortunately, little metabolic protection is present at the end of CPB when the patient is normothermic and when the risks of cerebral damage may be significant (see below). There has been a resurgence of interest in the use of normothermic CPB in some centres [19], although the effect on neurological outcome has yet to be documented.

The role of anaesthetic agents in organ protection during CPB, with or without hypothermia, remains uncertain. With thiopentone, unlike the effect of hypothermia, the maximum reduction in $CMRo_2$ is achieved when the EEG is isoelectric [20]. EEG suppression and reductions in $CMRo_2$ in adults may be produced at moderate hypothermia and at normothermia during CPB using thiopentone or isoflurane [6]. In 1986, Nussmeier, Arlund and Slogoff showed that thiopentone, titrated to EEG suppression throughout normothermic CPB (average dose 39.5 mg kg^{-1}), reduced the incidence of neurological damage after bypass [7], but its prolonged elimination half-life resulted in increased inotrope requirement after bypass and delayed tracheal extubation. A recent study indicates that high-dose thiopentone may also reduce overall mortality after CPB [21].

On the basis that "embolic" release is most likely to occur after aortic declamping, Metz and Slogoff showed that thiopentone 15 mg kg^{-1}, given as a bolus before declamping to produce EEG suppression, appeared to be as effective as a high-dose thiopentone infusion in preventing neurological damage. Extubation times were shorter in the bolus group, but inotropic requirements were similar [22]. Unfortunately, aortic declamping may not be the most dangerous time for air emboli, which commonly occur immediately after termination of CPB [23].

Propofol, in common with thiopentone has been shown to reduce $CMRo_2$ in normothermic patients [24, 25] and during CPB it can be titrated to produce EEG suppression during cooling, hypothermia (at 28 °C) and rewarming in adults [8]. The major advantage in using propofol as a metabolic depressant, rather than thiopentone, is its short half-life allowing rapid adjustment in depth of anaesthesia. In this study, as with the previous study in adults [8], EEG burst suppression was induced readily with propofol, within minutes from the onset of CPB. In theory, even more rapid EEG suppression could be achieved if the bypass circuit had been primed with propofol. However, rapid infusion of pump prime is often required if the patient is hypotensive before the onset of CPB and propofol could, potentially, worsen such a situation. Burst suppression was maintained easily during cooling and hypothermia; however, in some patients in both studies, burst suppression was difficult to maintain during rewarming, despite large increases in the propofol infusion rates. Subsequent experience with the use of propofol for "induction" and maintenance of cardiac anaesthesia in children, has shown that EEG burst suppression is easier to achieve and maintain in these circumstances [unpublished data].

The greater infusion rates required in children may be caused by increased volume of the bypass circuit, 50 % greater central compartment volume, 25 % greater clearance in children [26] and possible sequestration of propofol in the bypass circuit [27]. The blood concentrations of propofol needed to achieve burst suppression in children were also greater than those in adults [8], but different sampling sites were used in the two studies, and this can influence measured concentrations of propofol.

The propofol infusions were discontinued immediately before termination of CPB and restoration of the EEG to normal occurred 5–15 min after the end of CPB. In view of the incidence of air emboli at this time, it might be preferable to continue the propofol into the early period after CPB, providing cardiovascular variables are stable. Propofol acts as a vasodilator during CPB in adults [28] and may also decrease myocardial contractility [29]. While propofol had no apparent effect on mean arterial pressures in our study, this was complicated by the use of phenoxybenzamine to produce even cooling and rewarming in the younger children. Also, smaller mean arterial pressures are commonly seen in children during CPB. Further investigation is needed to clarify the vascular effects of propofol during CPB in children. There was no evidence that propofol increased inotrope requirements or prolonged recovery in this study.

Although previous metabolic studies with anaesthetic agents during CPB have concentrated on reductions in $CMRo_2$ [3], damage relating to CPB is multi-organ in nature [2], hence the need to study the effects of anaesthesia on $\dot{V}o_2$. While a reduction in $CMRo_2$ may contribute to a reduction in $\dot{V}o_2$, anaesthetic-induced metabolic depression occurs in many other organs [30], this being of potential benefit during CPB. In adults, $\dot{V}o_2$ is reduced by propofol [9], but not by isoflurane [31] during hypothermic CPB. This study in children showed significant increases in $S\bar{v}_{O_2}$ at hypothermia and normothermia and decreases in $\dot{V}o_2$ at normothermia in the propofol group, despite a slightly higher Do_2. The decrease in $\dot{V}o_2$ at hypothermia in this group was also nearly significant ($P < 0.07$). In the adult study [9], there were large decreases in systemic vascular resistance and slightly greater concentrations of lactate in the propofol group, possibly suggesting maldistribution of blood flow as a mechanism for the reductions in $\dot{V}o_2$. In this study, mean arterial pressures did not differ and lactate concentrations decreased in both groups during CPB, strongly suggesting direct metabolic depression as a mechanism for the changes in $S\bar{v}_{O_2}$ and $\dot{V}o_2$. The increase in lactate concentrations at the start of CPB were caused by the use of lactated Ringer's solution in the pump prime [32].

The "stress response" has been well documented in adults and children and is especially pronounced during CPB [3]. Catecholamines, cortisol and other vasoactive substances, including prostaglandins, are released which produce alterations in microvascular permeability and multi-organ damage [2, 3]. These hormone changes also result in hyperglycaemia, which is known to worsen neurological outcome after cerebral ischaemia [33]. The use of opioids alone can block the stress response in children before CPB [34, 35]. During CPB, the stress response may be attenuated by alfentanil, fentanyl, sufentanil, enflurane and isoflurane [3]. This effect appears to be related to the depth of anaesthesia and may be important in reducing the damaging effects of CPB [3]. It is not known if one particular agent is most effective in reducing the stress response, although fentanyl produces a more prolonged block of cortisol response than alfentanil [36]. Fentanyl is known to be taken up by membrane oxygenators and plasma concentrations are maintained better by continuous infusions [3]. In this study, we showed significant decreases in both glucose and cortisol in the propofol group. It is also interesting to note that there was little change in these responses during CPB in the control group. T3 concentrations are known to decrease after CPB in children [37] and this was not affected by the addition of propofol.

At the present time, thiopentone and other barbiturates continue to be given by some anaesthetists during high risk cardiac surgery, to reduce associated neurological damage, although their use remains controversial [38]; the use of other anaesthetic agents during CPB is more controversial [39], probably reflecting the lack of good data linking anaesthetic technique to improved outcome [40]. This study in children shows that propofol given by infusion can suppress the EEG during CPB, reduce $\dot{V}O_2$ at normothermia and reduce the glucose and cortisol responses to CPB. If increasing anaesthetic depth [3], metabolic depression [1] (particularly during rewarming and normothermia), prevention of hyperglycaemia [33] and attenuation of the stress response [3] are important in improving outcome after CPB, the use of propofol in combination with an opioid-based anaesthetic may be advantageous in reducing the unwanted effects of CPB. Further studies are now indicated to establish the safety and efficacy of propofol in high risk patients.

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INFUSION OF PROPOFOL TO IDENTIFY SMALLEST EFFECTIVE DOSES FOR INDUCTION OF ANAESTHESIA IN YOUNG AND ELDERLY PATIENTS

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SUMMARY

We studied 110 patients older than 60 yr or aged 18–50 yr as separate groups in two stages to identify the smallest effective doses of propofol for induction of anaesthesia. In the elderly patients, in stage 1, at infusion rates of 25, 50 or 100 mg min^{-1} *the mean (SD) doses administered were propofol 0.82 (0.14) mg* kg^{-1}, *1.22 (0.24) mg* kg^{-1} *and 1.65 (0.60) mg* kg^{-1} *and the induction times 140.1 (21.9) s, 103.2 (23.5) s and 69.4 (10.0) s, respectively. In stage 2, after induction with a fixed dose of 0.82 mg* kg^{-1} *as a bolus over 5 s or as an infusion at 25 mg* min^{-1}, *the times for induction were 38.5 (14.0) s and 144.5 (36.6) s, respectively. In the young patients, at induction rates of 33.3, 50, 100 or 200 mg* min^{-1}, *the doses administered were propofol 1.36 (0.28) mg* kg^{-1}, *1.46 (0.12) mg* kg^{-1}, *1.85 (0.43) mg* kg^{-1} *and 2.39 (0.50) mg* kg^{-1} *and the induction times 145.0 (25.4) s, 120.0 (18.4) s, 80.2 (19.2) s and 54.5 (10.4) s, respectively. In stage 2, a fixed induction dose of 1.46 mg* kg^{-1} *resulted in induction times of 35.0 (8.5) s and 134.0 (26.8) s, respectively. In stage 2 of each age group, induction was achieved with smaller doses than those recommended previously and there was no difference in the number of patients in whom induction of anaesthesia was successful or in the measured cardiorespiratory variables between the two induction regimens. This suggests the latter effects are caused by the dose administered and not the rate of administration.*

KEY WORDS

Anaesthetics, intravenous: propofol. Anaesthetic techniques, induction.

The effect of varying the rate of administration of propofol on dose requirements for induction of anaesthesia and on cardiovascular and respiratory stability has been studied in both elderly [1–3] and young [4–7] patients. In both studies using infusion techniques [1, 4] it was shown that induction of anaesthesia with propofol by slow i.v. infusion reduced the dose requirements, caused less decrease in systolic and diastolic arterial pressures and reduced the incidence of apnoea. This was thought to be because of the avoidance of a relative overdose of induction agent. The mechanisms proposed for this effect were that the slow infusion rate allowed time for the induction agent to reach its site of action with the slower circulation time in elderly patients [1] and that a finite transport time for the drug to reach the biophase is required [4].

We have examined further the effect of different rates of infusion of propofol on induction dose and cardiorespiratory changes in the two groups of patients. In particular, we wished to identify the smallest effective dose for each group and compare the cardiovascular responses when this dose was administered as a bolus or as a slow infusion.

PATIENTS AND METHODS

The present studies were conducted on two separate groups of patients: the first consisted of 50 patients aged 60 yr or older and the second, 60 patients aged 18–50 yr. All patients were of ASA class I or II and scheduled to undergo elective body surface surgery of 30–60 min duration, not requiring tracheal intubation. Local Ethics Committee approval was given and written informed consent obtained from each patient. Patients were excluded if they were more than 20% greater than ideal body weight or had a previous adverse response to general anaesthesia. Each study was conducted in two stages and all patients were premedicated with temazepam 20 mg orally 1 h before surgery. In the anaesthetic room, monitoring consisting of pulse oximetry, non-invasive arterial pressure and ECG was commenced and a cannula was inserted into a suitable vein. All patients received fentanyl 0.75 µg kg^{-1} i.v. as a bolus, 5 min before the start of induction. Cardiovascular recordings were made at the commencement of monitoring as a baseline measurement, at the end of

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induction and at 2 and 5 min after the end of induction.

Stage 1

The first stage was used to determine the smallest infusion rate which would provide an acceptable quality of induction, defined arbitrarily as a smooth induction occurring within 3 min of the start of the induction dose. Although complications (e.g. apnoea of duration greater than 30 s) or complaints from the patients (e.g. excessive duration of induction) were recorded, their presence did not exclude an acceptable induction. Thirty elderly patients were allocated randomly to receive infusion of propofol 25, 50 or 100 mg min^{-1} and 40 young patients received propofol 33.3, 50, 100 or 200 mg min^{-1} using an Ohmeda 9000 syringe pump. Induction of anaesthesia was defined as loss of verbal contact with the patient, which was taken as the cessation of continuous speech by the patient. In any patient in whom anaesthesia was not induced after 200 s, the rate of administration of propofol was increased (to 100 mg min^{-1} in the elderly or 200 mg min^{-1} in the young) until induction was achieved (and noted to be an unsuccessful induction). After induction was completed, anaesthesia was maintained with 66 % nitrous oxide in oxygen with an infusion of propofol at a rate equivalent to 6 mg kg^{-1} h^{-1} in the young patients and enflurane in the elderly patients. The induction time was taken as the time from the start of the infusion to loss of verbal contact with the patient and the induction dose as the amount of propofol administered in that time. End-tidal carbon dioxide measurement was used to detect the incidence of apnoea lasting more than 30 s. Arterial pressure, heart rate and oxygen saturation were recorded as described above.

Stage 2

After completion of the first part of the study, the mean induction dose as a function of body weight was calculated for each of the infusion rates (table II). The minimum dose which had successfully induced anaesthesia in 100 % of patients in each age group was used as a fixed dose for induction in the second part of the study. An additional 20 patients in each age group were allocated randomly to receive induction of anaesthesia using the calculated dose either by infusion at the same rate as used in stage 1 or administered over 5 s. Additional propofol was not administered to any patient until an observation period of 200 s had elapsed from the start of administration of the dose. If loss of consciousness occurred within this time, anaesthesia was maintained as in stage 1. If anaesthesia was not induced within the observation period, additional propofol was administered (as an infusion at 100 mg min^{-1} in the elderly or 200 mg min^{-1} in the young) until anaesthesia was achieved and the patient was classified as having an unsuccessful induction.

The patient details, dose and time for induction were recorded as in stage 1, with the incidence of apnoea. Arterial pressure, oxygen saturation and heart rates were again measured as in the first stage.

Statistical analysis

Statistical analysis was performed separately for each age group using ANOVA for comparisons in stage 1 between the groups at separate times and Student's t test between pairs of groups where significance was demonstrated ($P < 0.05$). In stage 2, Student's t test was used to compare data in the bolus and infusion groups. Repeat measures MANOVA was used to compare sequential arterial pressures, oxygen saturation and heart rates within groups in both stages. Patient response as indicated by successful inductions in stage 2 or the incidence of apnoea was compared using chi-square analysis (Fisher's exact test). Tests were performed on the SPSS.PC 3.0^{+} statistical package.

RESULTS

For each age group there was no significant difference in age, weight, ASA status or sex ratio between the groups in each stage of the study (table I).

Elderly patients

Stage 1. Anaesthesia was induced successfully in all patients using the technique described. The mean (SD) induction times were 140 (21) s, 103 (24) s and 69 (10) s, respectively, for the infusion rates of propofol 25, 50 and 100 mg kg^{-1} min^{-1} and were significantly different between the groups ($P < 0.01$ for all three comparisons). The mean weight-related dose of drug administered at loss of consciousness was also significantly less at the slower infusion rates (table II), being equivalent to propofol 0.82 (0.14) mg kg^{-1}, 1.22 (0.24) mg kg^{-1} and 1.65 (0.60) mg kg^{-1}, respectively, for the three infusion rates ($P < 0.01$ for all comparisons). There were no significant differences in heart rate, oxygen saturation, systolic or diastolic arterial pressures between the infusion rates. Within each group there was a significant difference ($P < 0.05$) in all these variables between baseline and end of induction. The numbers of patients with apnoea were one, one and four in the three infusion groups (25, 50 and 100 mg min^{-1}), respectively (ns).

Stage 2. The smallest successful mean induction dose in stage 1 was propofol 0.82 mg kg^{-1} administered at 25 mg min^{-1} and this dose was used in stage 2 to compare the effects of infusion or bolus administration. Anaesthesia was induced success-

TABLE I. *Patient characteristics (mean (range or SD))*

Group	Propofol infusion rate (mg min^{-1})	Age (yr)	Sex (M:F)	Weight (kg)
Elderly	25	72.0 (62–84)	7:3	74.3 (13.8)
	50	70.4 (62–78)	7:3	72.7 (16.3)
	100	69.7 (62–81)	9:1	75.1 (15.6)
	Bolus	74.9 (65–82)	9:1	68.9 (21.7)
	Infusion	73.4 (62–83)	6:4	71.6 (11.2)
Young	33.3	37.4 (24–50)	3:7	71.8 (16.4)
	50	35.2 (18–50)	4:6	68.6 (8.3)
	100	39.2 (21–49)	1:9	68.1 (8.1)
	200	32.7 (18–47)	5:5	76.2 (11.2)
	Bolus	35.2 (19–46)	6:4	74.3 (10.6)
	Infusion	36.9 (24–49)	3:7	74.1 (13.4)

TABLE II. *Induction times, doses and successful inductions (mean* (SD) *[range]).* *P < *0.05* (*chi-square*); ***P < *0.001* (*ANOVA*), †††P < *0.001* (*Student's* t *test*) *between rates within age groups*

Group	Propofol infusion rate (mg min^{-1})	Induction time (s)	Dose (mg kg^{-1})	Successful inductions
Elderly	25	140.1 (21.9) [112–175]***	0.82 (0.14) [0.59–1.10]	10
	50	103.2 (23.5) [62–156]	1.22 (0.24) [0.81–1.57]	10
	100	69.4 (10.0) [56–89]	1.65 (0.60) [1.06–3.15]	10
	Bolus	38.5 (14.0) [20–60]†††	0.82	10
	Infusion	144.5 (36.6) [97–204]	0.82	8
Young	33.3	145.0 (25.4) [125–198]***	1.36 (0.28) [0.90–1.72]***	7*
	50	120.0 (18.4) [100–150]	1.46 (0.12) [1.21–1.62]	10
	100	80.2 (19.2) [60–120]	1.85 (0.43) [1.32–2.91]	10
	200	54.5 (10.4) [40–75]	2.39 (0.50) [1.09–3.48]	10
	Bolus	35.0 (8.5) [20–45]†††	1.46	10
	Infusion	134.0 (26.8) [100–180]	1.46	10

fully in all 10 patients in the bolus group within the 200-s time limit. In the infusion induction group, the same calculated dose of propofol 0.82 mg kg^{-1} was administered at 25 mg min^{-1}, and eight out of 10 patients had anaesthesia induced successfully within the time limit, but this difference was not significant. The mean (SD) induction time from commencing administration of the drug to loss of verbal contact in those with successful induction of anaesthesia within the time limit was significantly longer in the infusion group (144.5 (36.6) s) compared with the bolus group (38.5 (14.0) s) (table II). None of the patients was apnoeic. Arterial pressure, heart rate and oxygen saturation were not significantly different between the groups, but were significantly different with time within each group ($P < 0.05$) between baseline and end of induction.

Young patients

Stage 1. Anaesthesia was achieved in all patients, but at the slowest rate of infusion of propofol (33.3 mg min^{-1}) only seven of 10 patients were asleep within the 200-s observation period ($P < 0.05$). Induction times (excluding those in whom anaesthesia was not induced within the time limit) were significantly longer at the slower infusion rates with mean (SD) times of 145.0 (25.4) s, 120.0 (18.4) s, 80.2 (19.2) s and 54.5 (10.4) s at rates of propofol 33.3, 50, 100 and 200 mg min^{-1}, respectively ($P < 0.001$). The mean induction doses were propofol 1.36 (0.28) mg kg^{-1}, 1.46 (0.12) mg kg^{-1}, 1.85 (0.43) mg kg^{-1} and 2.39 (0.50) mg kg^{-1}, respectively ($P < 0.001$). All doses were significantly different ($P < 0.001$), with the exception of the 33.3- *vs* 50-mg min^{-1} comparison (table II).

The baseline heart rate of the 200-mg min^{-1} group was significantly faster than those in the other three groups ($P < 0.05$). The only statistically significant difference between groups in the percentage change of heart rate from baseline was at 2 min after induction between the 33.3- and 50-mg min^{-1} groups ($P < 0.05$). Within the 50- and 200-mg min^{-1} groups there was a statistically significant decrease in heart rate with time expressed as the percentage change from baseline ($P < 0.05$), although this was not clinically significant.

There was no difference in percentage change of systolic or diastolic arterial pressure from baseline between the four groups. The decrease in systolic pressure with time in all four groups and diastolic pressure with time in the propofol 50-, 100- and 200-mg min^{-1} groups was significant ($P < 0.05$).

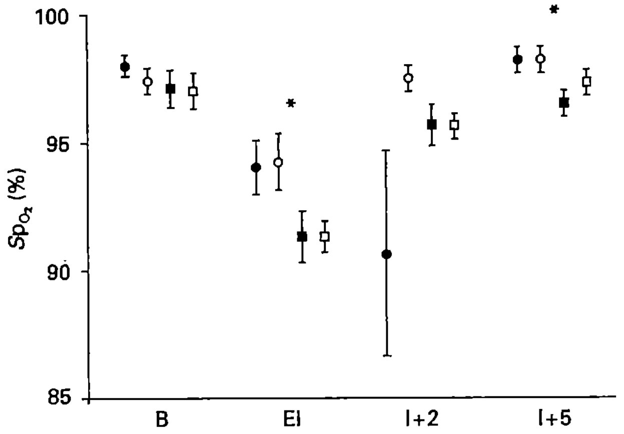

FIG. 1. Oxygen saturation (Sp_{O_2}) (mean, SD) during stage 1 in young patients. B = Baseline; EI = end of induction; I+2 = 2 min after induction; I+5 = 5 min after induction. ● = Propofol 25 mg min^{-1}; ○ = propofol 50 mg min^{-1}; ■ = propofol 100 mg min^{-1}; □ = propofol 200 mg min^{-1}.

There was a decrease in oxygen saturation with time in all four groups and this was significant in the 33.3-mg min^{-1} and the 200-mg min^{-1} groups ($P < 0.05$) (fig. 1). In addition, there were significant differences in oxygen saturation at the end of induction and 5 min after induction between the 100- and 200-mg min^{-1} groups and the 50- and 33.3-mg min^{-1} groups ($P < 0.05$). Five patients in the 200-mg min^{-1} group, six in the 100-mg min^{-1} group and three in the 33.3-mg min^{-1} group had apnoea, compared with none in the group receiving propofol 50 mg min^{-1} ($P < 0.05$).

Stage 2. The slowest rate of infusion in stage 1 which successfully induced anaesthesia in all patients was propofol 50 mg min^{-1}, with a mean dose of 1.46 mg kg^{-1}. This dose was used in stage 2 to compare the effects of infusion or bolus administration of a fixed dose.

Anaesthesia was induced successfully in all patients given propofol 1.46 mg kg^{-1} as a bolus or as an infusion at 50 mg min^{-1}. The mean (SD) induction time was significantly longer in the infusion group compared with the bolus group: 134.0 (26.8) s and

35.0 (8.5) s, respectively (table II). Three patients in the bolus group and none in the infusion group became apnoeic (ns).

Arterial pressures, heart rates and oxygen saturations were not significantly different at any time between the two groups. Systolic and diastolic arterial pressures were significantly different with time within each group ($P < 0.05$). Heart rate was significantly different with time in the bolus group ($P < 0.001$).

DISCUSSION

In the present studies, we have used smaller doses of propofol than those recommended previously [2, 3, 5–7]. The slowest infusion rate which successfully induced anaesthesia without the requirement for additional increments was propofol 50 mg min^{-1} in the young patients and propofol 25 mg min^{-1} in the elderly. These infusion rates resulted in doses of propofol 1.46 and 0.82 mg kg^{-1} being administered for induction in the respective age groups. When these doses were administered as a bolus over 5 s or as an infusion at the respective rate, all patients in the younger group had anaesthesia induced successfully. In the elderly group, all the bolus group had successful induction of anaesthesia, but only eight of 10 in the infusion group (ns). There were no significant differences in cardiorespiratory measurements between the bolus or infusion administration within each age group.

Our study in the younger patients differed from that of Stokes and Hutton [4] in that a slower infusion rate (33.3 mg min^{-1}) was used and the bolus administered was the smallest dose defined by the infusion study (1.46 mg kg^{-1}), rather than a predefined dose (2 mg kg^{-1}). The results for the young patients in the present study are similar to those of Stokes and Hutton [4], who used twice the dose of fentanyl compared with the present study. Their induction doses were propofol 1.40, 1.96 and 2.61 mg kg^{-1} at infusion rates of 50, 100 and 200 mg min^{-1}, compared with doses of propofol 1.46, 1.85 and 2.39 mg kg^{-1} at the same rates in the present study. The addition of a slower infusion rate (33.3 mg min^{-1}) in the present study increased further the time for induction, but with little reduction in the dose administered (1.36 mg kg^{-1}) and three of 10 patients did not have anaesthesia induced within the observation period. In the younger age group, it would appear that, by reducing the rate of administration of propofol, the smallest effective dose for induction of anaesthesia in younger patients was being reached. Beyond a limit, induction becomes unacceptable as the patients start to breath-hold and arterial desaturation may occur. This effect was seen between the four groups in stage 1 in the younger patients. The slower infusion rates (33.3 and 50-mg min^{-1}) were associated with a greater oxygen saturation at the end of induction than the faster rates, but in the propofol 33.3-mg min^{-1} group the oxygen saturation decreased because of breath-holding. In contrast, no patient in the propofol 50-mg min^{-1} group became apnoeic and this group had the smoothest induction and required no interventions because of desaturation (fig. 1).

Our previous study in elderly patients [1] had shown that smaller doses of propofol could be used successfully for induction of anaesthesia when given as an infusion. Associated with this was a reduction in the percentage decrease in arterial pressure at the slower infusion rates. The results for the induction dose and induction time for the two infusion rates which were repeated in the two elderly studies were comparable. The propofol 100 mg min^{-1} infusion values were 1.60 mg kg^{-1} in 67 s and 1.65 mg kg^{-1} in 67 s for the two studies and those for the 50-mg min^{-1} infusion were 1.24 mg kg^{-1} in 104 s and 1.22 mg kg^{-1} in 103 s. These results suggest that an infusion technique is reproducible in patient groups of a similar age receiving the same premedication. The further reduction in infusion rate in the first part of the study in elderly patients has shown that even smaller doses of propofol can be used for induction of anaesthesia. Slower infusion rates were not used in the elderly, as previous attempts had resulted in induction times longer than 200 s, and this was felt to be unsuitable for standard anaesthetic practice.

When the smallest infusion dose was used in the second part of the study to compare a fixed dose administered as a slow infusion against bolus administration, there was no significant difference between any of the recorded measurements except the time for induction. In the elderly, all patients in the bolus group had anaesthesia induced successfully in a mean time of 38.5 s, whilst the infusion group (propofol 25 mg min^{-1}) were induced in a mean time of 145.5 s, which excluded two patients who had not been induced within the 200-s time limit and required additional drug to complete induction. The difference in the success rates of the two induction regimens can be explained because the dose value of 0.82 mg kg^{-1} was derived from a mean dose in the first stage. It is not surprising, therefore, that two of the 10 patients required more than the fixed dose to complete induction. In stage 2 for the young patients, the calculated smallest dose (1.46 mg kg^{-1}) was again given as a 5-s bolus or as an infusion at 50 mg min^{-1}. There were no significant differences in the recordings between the two groups except that, again, the induction time was significantly greater with the infusion (134 s compared with 35 s). All the patients had anaesthesia induced successfully, but three in the bolus group were apnoeic, compared with none in the infusion group (ns). By using the infusion technique to identify a smallest dose in each age group and then comparing the efficacy when those fixed doses are administered as a bolus or as an infusion, it would appear that we have identified mean doses, which reliably induce anaesthesia, that are much smaller than those reported previously, and have shown that cardiovascular changes occur in response to the amount of drug administered and not the rate of administration.

Gillies and Lees [6] have shown previously that induction with equipotent doses of etomidate or propofol at equivalent injection rates produced slower induction times with propofol compared with etomidate. This difference in induction times is related to the "biophase kinetics" described by Hull

[8]. Stokes and Hutton [4] commented that a "biophase delay" may be the rate limiting factor in onset of induction with propofol and may explain how induction is achieved with smaller doses of propofol at slower infusion rates. However, the same effect has also been demonstrated for thiopentone, with which reduced doses are required to induce anaesthesia at slower infusion rates [9]. The mean induction times in the two bolus groups were similar (35 s in young patients compared with 38 s in elderly patients), despite different doses being administered in the two age groups (propofol 1.46 and 0.82 mg kg^{-1}). This would suggest that there are no major differences in the rate of drug delivery within the body (differences in circulation time or biophase delay) between the two age groups. Thus the difference in doses is likely to be caused by changes in the distribution of drug within the body. In part, this is produced by a reduction in the initial volume of distribution, resulting in greater concentrations in elderly patients, as demonstrated by Kirkpatrick [10]. However, this may not be the complete answer, as the dose in the elderly as a proportion of the younger patients' dose administered in the present study was 56%, compared with 75% of the initial volume of distribution reported by Kirkpatrick and colleagues [10]. Other factors which may play a part are changes in the relative distribution of cardiac output or in the cellular responsiveness to the drug.

It is also worth noting that the induction times for the bolus groups were approximately 40 s, which is twice the initial observation period used by Dundee and colleagues [2] in their assessment of dose requirements in different patient groups. This may in part explain the smaller dose required in the present study, but the effect of premedication with temazepam and fentanyl, which were not used by Dundee and his colleagues, must contribute to this also. This suggests that a longer period of observation should be used with slower rates of injection in dose–response studies investigating the dose of drug required to induce anaesthesia.

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I.V. BOLUS ADMINISTRATION OF SUBCONVULSIVE DOSES OF LIGNOCAINE TO CONSCIOUS SHEEP: EFFECTS ON CIRCULATORY FUNCTION

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SUMMARY

We have studied the effects of subconvulsive doses of lignocaine on circulatory function in five conscious, chronically instrumented sheep. In the absence of overt signs of central nervous system toxicity, 50-, 75- or 100-mg i.v. bolus doses of lignocaine induced reductions in myocardial contractility, as assessed by the maximum rate of increase in left ventricular pressure (LV dP/dt_{max}*), of 17 (*SD *4)%, 25 (4)% and 33 (4)%, respectively. The durations of these reductions in myocardial contractility were 2–3.5 min. There were no significant changes in cardiac output, coronary artery blood flow, mean arterial pressure, heart rate or left ventricular systolic and diastolic pressures. It is concluded that the initial toxic effects of lignocaine are on the heart rather than the central nervous system, as is generally believed. This negative inotropic effect of lignocaine* in vivo *may be more deleterious to myocardial function when the heart is compromised by pre-existing disease, or the co-administration of other myocardial depressive drugs.*

KEY WORDS

Anaesthetics, local: lignocaine. Complications: subconvulsive dose. Heart: myocardial depression.

Lignocaine is a widely used local anaesthetic and a class I antiarrhythmic agent, effective for the treatment of ventricular arrhythmias in ischaemic heart disease and after cardiac surgery. When used i.v., it has a narrow margin of safety [1–4]. Toxic effects on the central nervous and cardiovascular systems are most obvious after accidental i.v. injection [5, 6]. Previous studies of lignocaine toxicity have found that cardiovascular system collapse usually occurred after the appearance of central nervous system toxicity; the latter was usually manifested as drowsiness, seizures and convulsions [7–12]. Based on this, it is believed generally that the cardiovascular system is more resistant than the central nervous system to the toxic effects of lignocaine [5, 8, 10, 13, 14]. However, there are reports of deterioration in cardiovascular function in the absence of central nervous system toxicity in both experimental animals and patients [5, 15]. Furthermore, it is known that the central nervous system effects of lignocaine can stimulate the sympathetic nervous system, thereby exciting the cardiovascular system and "overriding" the toxic effects of lignocaine on the latter system [16, 17]. Animal studies have also suggested that blood drug concentrations large enough to produce cardiac toxicity may be reached after the i.v. bolus doses of lignocaine recommended for the treatment of cardiac arrhythmias [4]. Therefore, this study was designed to examine the effects of i.v. lignocaine in bolus doses between those suggested for the treatment of cardiac arrhythmias and those that are known to cause central nervous system toxicity.

MATERIALS AND METHODS

The study was approved by the institutional Ethics Review Committee. We studied five adult merino ewes weighing between 37 and 52 kg. Three studies (one for each drug dose) were performed in each of the sheep, which had been prepared previously with chronic intravascular catheters and Doppler flow probes to allow drug administration, cardiovascular function monitoring and measurement of blood flow. All animals had free access to food and water throughout the study.

Animal preparation

The sheep were prepared in two stages. Two weeks before experimentation, sheep were anaesthetized with i.v. thiopentone 20 mg kg^{-1} and the trachea intubated with a cuffed tracheal tube (Size 9; Portex Ltd, Hythe, England). Anaesthesia was maintained with 1.5% halothane and 60% nitrogen in oxygen and end-expiratory carbon dioxide was monitored by an infra-red carbon dioxide analyser (Normocap, Datex Instrumentarium Co., Finland) and maintained in the range 4–4.5%. A left thoracotomy at the 4th intercostal space and a pericardiotomy were performed to expose the pulmonary artery and the left main coronary artery. Doppler flow probes (Titronics Medical Instruments, Iowa City, Iowa, U.S.A.) were placed around the left main coronary artery and pulmonary artery. The leads of the probes were exteriorized through the chest

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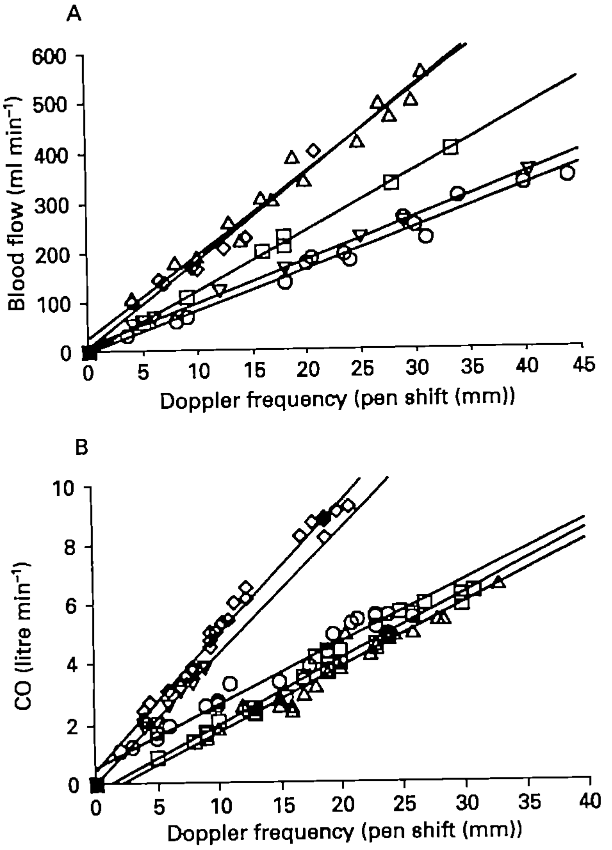

FIG. 1. A: *In vitro* calibration of the Doppler flow probes on the left main coronary artery. Left coronary artery blood flows were measured using the beaker and stopwatch method and Doppler frequency shifts were expressed as pen shifts on the chart recorder, which was calibrated so that 20 mm of pen shift equalled 4 kHz of Doppler frequency shift. B: *In vivo* calibration of the Doppler flow probes on the pulmonary artery. Cardiac outputs (CO) were measured using a thermodilution method and Doppler frequency shifts were expressed as pen shifts on the chart recorder, which was calibrated so that 40 mm of pen shift equalled 4 kHz of Doppler frequency shift. Each line represents data from one sheep.

incision and a subdermal tunnel. The incisions were closed with silk sutures and the sheep allowed to recover from anaesthesia.

One week later, the sheep were anaesthetized as described above for catheterization of various blood vessels using a modification of the method reported previously [18, 19]. The right carotid artery and jugular vein were exposed via a neck incision. Using the Seldinger technique, two 7-French gauge (Multi-purpose A1 catheter, Cordis Corporation, Miami, FL, U.S.A.) and a 9-French gauge (William A. Cook, Sydney, N.S.W., Australia) catheters were placed in the ascending aorta, with their tips located approximately 2 cm above the aortic valves via the carotid artery. Through the jugular vein, a 7-French gauge catheter (Multi-purpose A1 catheter, Cordis Corporation) was placed in the inferior vena cava (IVC), a quadripolar intracardiac ECG wire (USCI Ltd, Billerica, MA, U.S.A.) and a 7-French gauge catheter (Multi-purpose B1 catheter, Cordis Corporation) in the coronary sinus and a flow-directed thermodilution catheter (Swan–Ganz, Edwards Laboratories, Irvine, CA, U.S.A.) in the pulmonary artery. The positions of these catheters were confirmed under direct vision using a fluoroscope with the injection of radio-opaque contrast (Conray 420 (70 % iothalamate), May and Baker Ltd, Dagenham, U.K.) into the corresponding blood vessels. All the surgical procedures were performed using sterile technique. Methadone 10 mg was given s.c. for postoperative pain management. Studies were not started until 1 week later, so that the sheep could recover fully from surgery, and to allow the Doppler flow probes to become firmly embedded in scar tissue—this ensured good acoustic coupling [20, 21]. The catheters were continuously flushed with heparinized (5 iu ml^{-1}) 0.9 % saline at a rate of 3 ml h^{-1}, using a gas powered system [18]. The sheep were housed in metabolic crates.

Cardiovascular function and blood flow measurements

During the experiments, the Doppler frequency shifts from both Doppler flow probes were obtained using a four-channel Doppler Flowmeter (Bio-engineering, The University of Iowa, 56 M.R.F. Iowa City, Iowa, U.S.A.) and a high frequency response (700-Hz) ink-jet chart recorder (Mingograf82, Siemens–Elema, Solna, Sweden; hereafter termed the chart recorder). The pulmonary artery Doppler flow probes were calibrated *in vivo* by correlating the pulmonary artery Doppler shifts with the cardiac outputs determined simultaneously by the standard thermodilution method using the thermodilution catheter placed in the pulmonary artery and a cardiac output computer (Model 9520A, Edwards Laboratories Inc., Irvine, CA, U.S.A.), as described previously [22]. During the calibration, sheep were anaesthetized and undergoing artificial ventilation as described above. Cardiac output was varied by changing the concentrations of inhaled halothane. The left coronary artery Doppler probes were calibrated *in vitro* at the termination of the studies, using the beaker and stopwatch method [20, 21].

Mean arterial pressure was measured using a pressure transducer (Model 4-327-I, Bell and Howell Inc., Pasadena, CA, U.S.A.) connected via polyethylene pressure tubing (PT 36, Sorenson Research Co., Salt Lake City, UT, U.S.A.) to one of the 7-French gauge arterial catheters in the ascending aorta.

Immediately before an experiment, a 5-French gauge Millar Mikro-Tip pressure transducer catheter (Millar Instruments Inc., Houston, Texas, U.S.A.) was introduced, using sterile technique, into the left ventricle of the sheep via a Touhy–Borst adaptor (William A. Cook, Sydney, N.S.W., Australia) and the 9-French gauge catheter placed previously in the aortic arch. The left ventricular pressure measured using the Millar catheter was recorded on the chart recorder. The pressure signals were sent also to an analogue differentiator (Model 3640, Devices Pty Ltd, Sydney, N.S.W., Australia) and the differentiated signal, the rate of left ventricular pressure increase (LV dP/dt), was recorded also on the chart recorder. The positive peak value of LV dP/dt represents the maximum rate of left ventricular pressure increase (LV dP/dt_{max}), and this was used as an index of myocardial contractility.

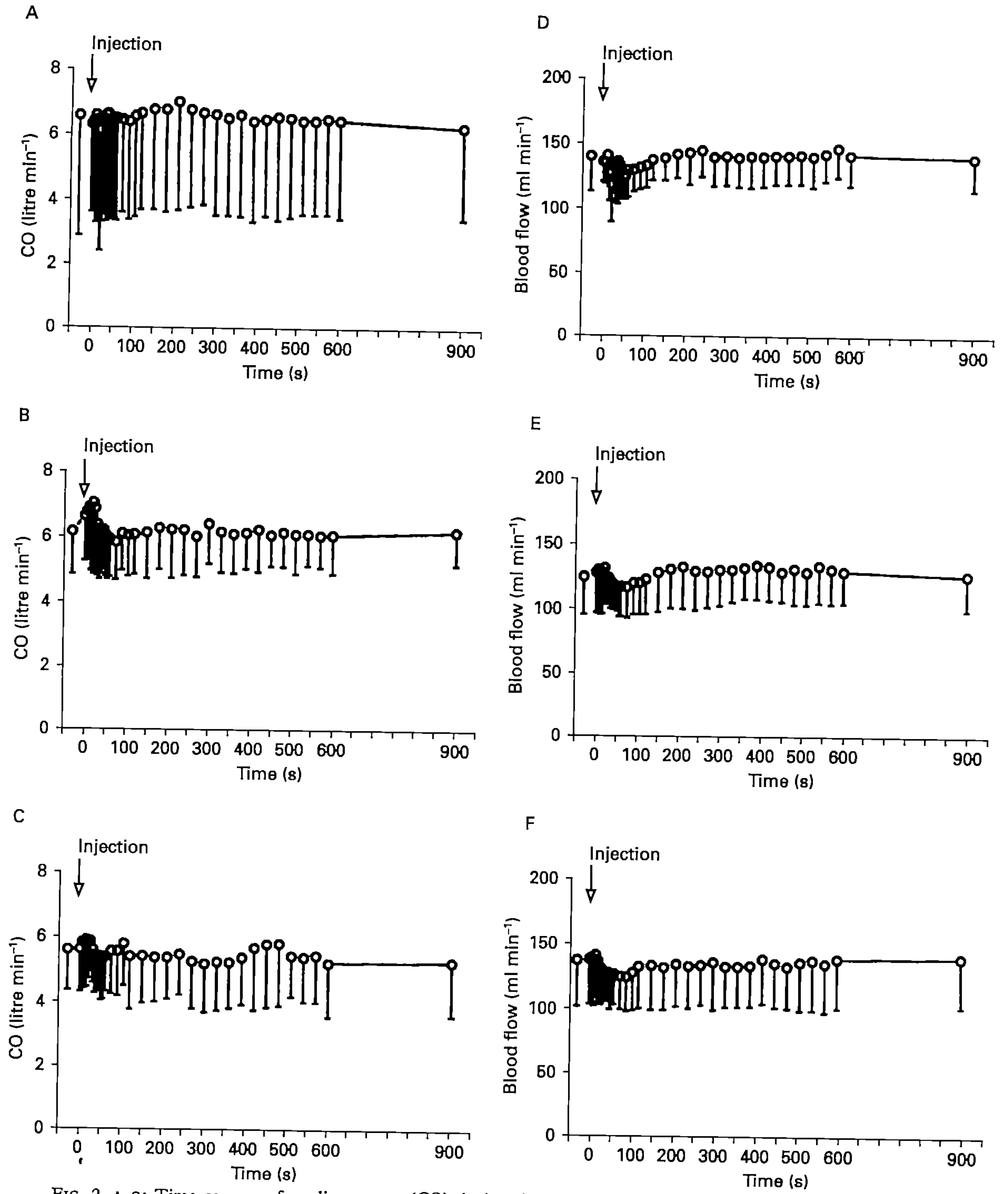

FIG. 2. A–C: Time-courses of cardiac output (CO) during the baseline recording periods and after the i.v. bolus injection (arrows) of lignocaine 50, 75 and 100 mg, respectively. D–F: Time-courses of left coronary artery blood flow during the baseline recording periods and after the i.v. bolus injection (arrows) of lignocaine 50, 75 and 100 mg, respectively. There were no significant changes in either of these variables after drug injections.

The response of this system was linear in the range 0–4000 mm Hg s^{-1}.

The intracardiac ECG was measured using the ECG wire placed in the coronary sinus, and was recorded using the chart recorder. Heart rate at a given time interval was obtained by multiplying the number of QRS complexes recorded over 6 s by 10.

Study design

Lignocaine was used in doses of 50, 75 or 100 mg. The order in which the doses were given to each sheep was selected randomly. At least 24 h was allowed between two studies in the same sheep. The selected doses were diluted to 10 ml with 0.9% saline immediately before an experiment.

During the experiments, the sheep were supported in a comfortable sling inside their metabolic crates in order to minimize movement that would influence the haemodynamic measurements. After the placement and the calibration of the haemodynamic measurement devices, sheep were allowed to settle for approximately 30 min. Baseline measurements of the haemodynamic variables were recorded on the chart recorder, at a paper speed of 25 mm s^{-1} for approximately 30 s. One of the selected lignocaine doses was injected into the IVC of the sheep over 1 s using an angiographic injector (Angiomat 3000, Viamonte Hobbs, Barber–Colman Company, Rockford, Illinois, U.S.A.). The haemodynamic variables were recorded continuously for the next 10 min, and for 30 s at 15 min after drug injection. It was known from previous studies that the cardiovascular system and central nervous system effects of these doses of lignocaine are no longer discernible by 10 min after injection in conscious sheep [12].

In addition to the haemodynamic measurements, the sheep were observed closely for any manifestation of central nervous system toxicity, such as agitation, excessive salivation, tremors or convulsions.

Data handling and statistical analysis

All the haemodynamic variables were measured every 5 s in the first 1 min after drug injection, every 15 s in the second 1 min, every 30 s until 10 min and for 30 s at 15 min after the injection. They were compared with baseline values recorded during the 30-s period immediately before drug injections. Double product, an index of myocardial oxygen consumption, was calculated as the result of left ventricular systolic pressure multiplied by the heart rate.

The rank sum two-sample test was used for statistical analysis of the differences in haemodynamic variables between the baseline values and the values recorded after drug injection. Linear regression was used for Doppler probe calibrations to correlate the pulmonary artery and coronary artery Doppler shifts with the cardiac outputs measured by the thermodilution method and coronary blood flow measured by the beaker and stopwatch method, respectively. The dose–effect relationships were also analysed by linear regression. $P < 0.05$ was considered statistically significant.

RESULTS

Cardiac output and coronary artery blood flow

The linear relationships between pulmonary artery Doppler frequency shift and cardiac output measured *in vivo* with the thermodilution method, and between left coronary artery Doppler frequency shift and left coronary artery blood flow measured *in vitro* with the beaker and stopwatch method are shown in figure 1. The correlation coefficients (r) ranged from 0.97 to 0.99 and from 0.98 to 0.99 for pulmonary artery and left coronary artery Doppler probe calibrations, respectively, for the five sheep. Therefore, linear regression was performed on each set of the calibration data and the individual slope and intercept were used for converting the recorded pulmonary artery or left main coronary artery Doppler shifts to cardiac output or left coronary artery blood flow in each sheep.

The time-courses of cardiac output and left coronary artery blood flow after i.v. injection of 50-, 75- or 100-mg doses of lignocaine are shown in figure 2. It is apparent that lignocaine did not change the cardiac output (fig. 2A–C). Although there was a small increase in mean values of cardiac output a few seconds after injection of lignocaine 75 mg (fig. 2B), these variations were not statistically different from baseline values. After each injection, there was a consistent, slight decrease in mean left coronary artery blood flow during the first 120 s (fig. 2D–F). However, these changes were not statistically different from the baseline values.

Myocardial contractility

The time-courses of LV dP/dt_{max} after i.v. bolus injection of lignocaine 50, 75 or 100 mg are shown in figure 3. All doses induced consistent decreases in LV dP/dt_{max}, and these changes were statistically different from the baseline LV dP/dt_{max} values. The durations of the period for which LV dP/dt_{max} were decreased statistically by each dose of lignocaine are shown in table I. The maximum depression of LV dP/dt_{max} was calculated as the mean (SD) of the two smallest values for each of the five studies ($n = 10$), and expressed as percent reduction from the baseline

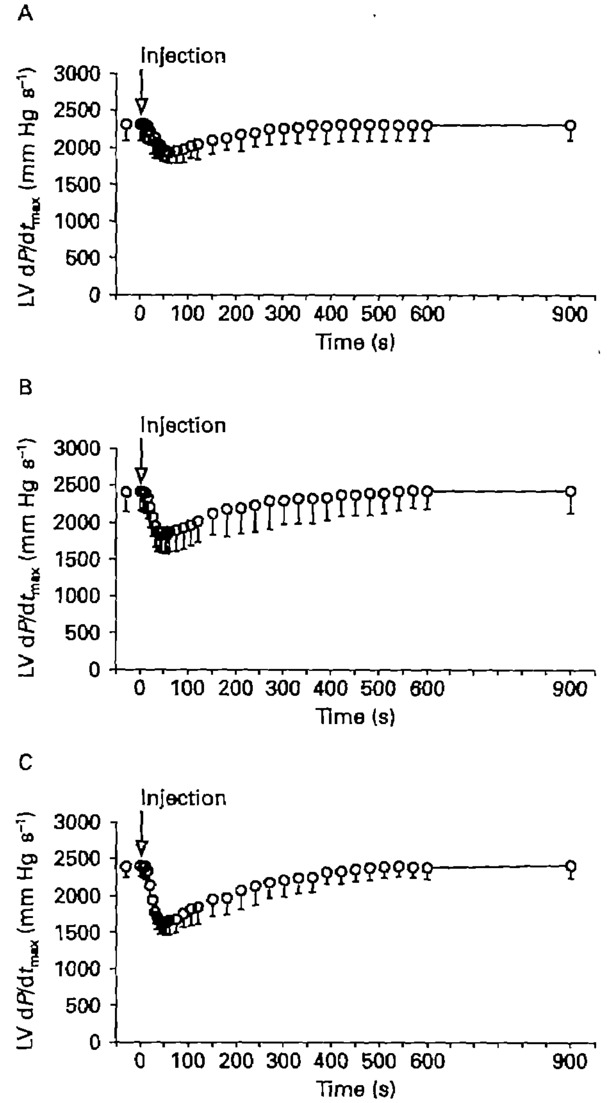

FIG. 3. A–C: Time-courses of LV dP/dt_{max} after the i.v. bolus injection (arrows) of lignocaine 50, 75 and 100 mg, respectively.

TABLE I. *Duration of the period of statistically significant reductions in LV* dP/dt_{max} *after i.v. injection of lignocaine, the maximum reduction in LV* dP/dt_{max} *expressed as percent from baseline values* (n = *10*) *and the time after the dose of this maximum reduction* (n = *5*) (*mean* (*SD*))

Dose (mg)	Duration (s)	Maximum reduction (% from baseline)	Time of maximum reduction (s)
50	140	17 (3.8)	51 (8)
75	130	24.9 (3.6)	50 (10)
100	220	32.6 (4)	45 (5)

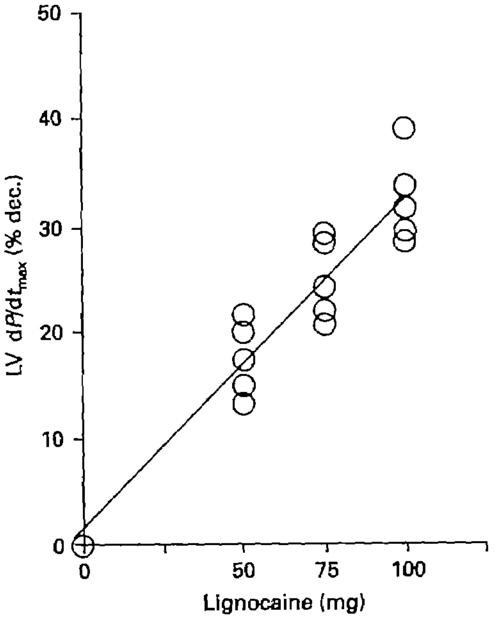

FIG. 4. Linear relationship between the maximum percent reductions in LV dP/dt_{max} and the lignocaine doses (0 = control), $n = 15$. Correlation coefficient (r) = 0.92; a (intercept) = 1.45; b (slope) = 0.31.

value. These values and the times at which the maximum depressions were first recorded are also listed in table I.

The dose-dependent nature of the depressive effect of lignocaine on LV dP/dt_{max} is shown by the linear correlation between the doses used and the maximum percent decreases in LV dP/dt_{max} observed (fig. 4). The correlation coefficient of this relationship (r) was 0.92.

Other haemodynamic variables

The heart rate, mean arterial pressure, left ventricular systolic and end-diastolic pressures and the calculated double product did not change significantly from the corresponding baseline values after i.v. bolus injection of each of the doses of lignocaine.

Central nervous system effects

In all animals and with all the doses used, there was no discernible central nervous system toxicity.

DISCUSSION

Since the introduction of lignocaine [23–25], there have been many detailed investigations of its adverse effects on the central nervous and cardiovascular systems. Both *in vitro* experiments using myocardial tissue or isolated perfused heart preparations [24, 26, 27] and *in vivo* experiments in anaesthetized animals [28–30] have confirmed the depressant effect of lignocaine on myocardial contractility. Central nervous system toxic effects of lignocaine have been observed also in animals and patients [11]. It is known that, in conscious animals, the central and sympathetic nervous systems are excited in the early stages of lignocaine toxicity [11], which in turn stimulates cardiovascular function [14, 17, 29]. Thus, despite the demonstrated negative inotropic effects of lignocaine *in vitro*, *in vivo* toxicity is often characterized by apparent positive inotropic effects. Because lignocaine is used in patients with a variety of pathological conditions, the importance of understanding the relative toxicity of the drug to the central nervous system and cardiovascular system has been emphasized [10].

In the present study, the central nervous system toxic effects were avoided by choosing doses of lignocaine between the "loading" dose which is often given as an i.v. bolus clinically for the treatment of arrhythmias [31, 32] and the doses which induced convulsions in conscious sheep [12]. In the absence of discernible convulsions or excitatory adverse central nervous system effects as reported in other studies [12], i.v. bolus injection of lignocaine 50, 75 or 100 mg produced significant negative inotropic effects on the myocardium of our sheep, as shown by decreases in LV dP/dt_{max} (fig. 3). It is known that simultaneous changes in heart rate and mean arterial pressure can influence LV dP/dt_{max} when used as an index of myocardial contractility [33]. However, these two variables did not change significantly from baseline values after injection of lignocaine, implying that the observed decreases in LV dP/dt_{max} were reflections of depression of myocardial contractility. Furthermore, the extent of this effect on myocardial contractility was linearly dose-dependent (fig. 4). This is consistent with a previous *in vitro* study which also showed that the reduction in myocardial contractile force induced by lignocaine was dose-dependent [27].

It has been concluded that the cardiovascular system is more "tolerant" to the toxic effects of i.v. lignocaine than the central nervous system [5, 7–9]. In most of these studies, conscious animals showed central nervous system toxicity, such as convulsion, before any deterioration in cardiovascular function. Cardiovascular collapse, as shown by the absence of an arterial pressure or electrical activity of the heart, was used as the indicator of cardiovascular toxicity [9, 10, 34]. However, in the presence of central nervous or sympathetic system excitation, such cardiovascular collapse should be viewed only as the end stage of the cardiovascular toxicity of lignocaine.

Although the doses of lignocaine used in the present study produced reductions in myocardial contractility (LV dP/dt_{max}) of up to 17–34% that lasted for approximately 2–3.5 min (table I), they did not change the haemodynamic variables monitored commonly in clinical practice (such as cardiac output, mean arterial pressure, left ventricular pressures and heart rate). It is not possible to determine from this study to what extent this "subclinical" reduction in myocardial function may influence patients receiving lignocaine. However, it would be expected that this effect would be more harmful when myocardial function is compromised, such as after myocardial infarction or the previous use of drugs such as calcium antagonists, barbiturates or some inhalation anaesthetics that are known to depress myocardial function. In these situations, the cardiovascular system may not be more tolerant to the toxic effect of lignocaine than the central nervous system. This argument is corroborated by the study of deaths from local anaesthetic-induced convulsions in which the median convulsant and lethal doses of lignocaine were similar in mice [35]. If these findings are applicable to humans, close monitoring of the haemodynamic status of patients is suggested, even when the recommended therapeutic dose of lignocaine is administered as an i.v. bolus. It could also be proposed that the practice of treating lignocaine toxicity with drugs, such as thiopentone or diazepam, that abolish convulsions may unmask or exacerbate the underlying myocardial depression caused by lignocaine.

It is noted that the rate of injection in this study was relatively rapid. However, rapid bolus injections are made in treating arrhythmias and may occur in cases of inadvertent i.v. injection for local anaesthesia [6]. Moreover, this injection rate is similar to those used in other studies [4]. Previous work in our laboratory has shown that the initial drug concentrations produced after an i.v. bolus are inversely related to cardiac output [36]. The conscious sheep used in these studies had relatively high cardiac outputs—we would expect the results obtained in this study to be close, in this respect, to those obtained in critically ill patients with lower cardiac outputs in which slower, more clinically relevant injection rates were used.

The slight reductions in arterial pressure and heart rate observed by other researchers in anaesthetized dogs [30, 37] were not observed when these doses of lignocaine were administered to conscious, unrestrained sheep in our studies. Therefore, the proposed "protective effect" of the i.v. use of lignocaine on the ischaemic myocardium (postulated to occur from a reduction in myocardial oxygen consumption as deduced from decreased values of double product [30]) was not seen in our preparation. Furthermore, continuous recording with the Doppler flow probe did not show any increase in left main coronary artery blood flow after the use of lignocaine in conscious sheep as was found in anaesthetized dogs [30], although it is noted that the doses and injection rates of lignocaine used in those studies were similar to those used here. These proposed protective effects on ischaemic myocardium may occur only under anaesthesia.

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EFFECT OF GRADED INFUSION RATES OF PROPOFOL ON REGIONAL AND GLOBAL LEFT VENTRICULAR FUNCTION IN THE DOG†

R. M. PUTTICK, J. DIEDERICKS, J. W. SEAR, J. B. GLEN, P. FOËX AND W. A. RYDER

SUMMARY

We have studied the effects of graded infusion rates of propofol (0.2–0.5 mg kg^{-1} min^{-1}) on left ventricular global and regional function, in eight acutely instrumented dogs. Global function was assessed by measurement of aortic and left ventricular pressure, LV dP/dt_{max}*, aortic blood acceleration and stroke volume. Regional function was assessed by measurement of systolic shortening and the end-systolic pressure–length relationship. The response of the coronary circulation to short periods of occlusion was also assessed. Administration of propofol significantly reduced left ventricular preload, as indicated by reductions in end-diastolic pressure and length; contractility was depressed, the depression being greater in the apex than in the base of the left ventricle. High infusion rates impaired relaxation. Regulation of coronary blood flow was not disrupted. Reductions in preload and contractility contributed to the propofol-induced hypotension. After 60 min, recovery from the greatest infusion rate was incomplete.*

KEY WORDS

Anaesthetics, intravenous: propofol. Arteries: coronary circulation. Heart: left ventricular function.

Propofol has been reported to decrease arterial pressure, systemic vascular resistance, cardiac output and stroke volume [1–4]. The most consistently reported effect of propofol on heart rate is a reduction thought to be caused by a resetting of baroreceptors to allow slower heart rates despite decreases in arterial pressure [5].

The mechanisms thought to account for the hypotension include peripheral vasodilatation, reduced ventricular filling and a depression in contractility. Glen and Hunter [6] demonstrated that administration of propofol to mini-pigs produced peripheral vasodilatation and, originally, this appeared to be the main determinant of propofol-induced hypotension. More recently, systemic vasodilatation was demonstrated when propofol was administered during cardiopulmonary bypass [7]. In contrast with these studies, other investigators have found systemic vascular resistance to be essentially unchanged by propofol [8]. Goodchild and Serrao [9] found an increase in venous capacitance in vagotomized dogs with pharmacologically denervated hearts. This venodilatation is dose-dependent and may contribute to hypotension through reduction of the preload. In the same study, it was shown that large concentrations of propofol caused both peripheral vasodilatation and myocardial depression. In addition to changes in venous capacitance and peripheral vascular resistance, a decrease in myocardial contractility may also contribute to the decreased arterial pressure. Indeed, Carlier and colleagues [8] showed that propofol reduced stroke volume with little effect on left ventricular filling pressure, which suggests a depressant effect on myocardial contractility. At a cellular level, propofol has been shown to reduce influx of calcium into guineapig isolated ventricular myocytes [10], thereby decreasing contractility. Another possible factor contributing to the negative inotropic effect is the reduction of catecholamine release by propofol [11].

The aim of this study was to determine the effects of graded doses (infusion rates) of propofol on the cardiovascular system, with particular reference to myocardial function. From the clinicians' point of view, there are few studies describing the dose–concentration–effect relationships for i.v. agents. Sear and Prys-Roberts [12] proposed the "minimum infusion rate" (MIR) and multiples thereof as one possible index to describe the potency of doses of i.v. agents. However, use of infusion rates as the indicator of dose ignores the kinetic variability that exists for i.v. agents (and hence the differences between predicted and measured drug concen-

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trations) [13]. Hence, we have also examined the concentration–effect relationships for propofol in this study.

MATERIALS AND METHODS

This study conformed to the Animals (Scientific Procedure) Act of 1986 (U.K.; Home Office license no PPL 30/00296). Eight dogs of both sexes, mean weight 20.3 kg (range 15.9–22.7 kg) were premedicated with morphine 0.1 mg kg^{-1} and anaesthetized with thiopentone 15–20 mg kg^{-1} i.v. The trachea was intubated, the animal placed on the right side, and the lungs ventilated with 70% nitrogen in oxygen at a rate of 12 b.p.m. with a tidal volume of 30 ml kg^{-1}. Oxygen concentration was monitored continuously by paramagnetic analysis. Carbon dioxide was added to the mixture to maintain the end-tidal carbon dioxide concentration at 5.3% as measured continuously by an infra-red carbon dioxide analyser. During the surgical procedure anaesthesia was maintained with 0.7–1.5% halothane using a Fluotec vaporizer (Cyprane, Keighley, U.K.). Mid-oesophageal temperature was monitored and maintained at 36–37 °C using a servo-controlled heating element incorporated into the operating table. An i.v. cannula was inserted via the femoral vein into the inferior vena cava for constant infusion of isotonic sodium chloride (0.154 mol $litre^{-1}$; 37 °C) at a rate of 5 ml kg^{-1} h^{-1}. Limb lead II of the ECG was recorded throughout the investigations.

The left common carotid artery was isolated in the neck, and a rigid 8-French gauge (2.76-mm o.d.) cannula, connected to a Druck pressure transducer (Druck Ltd, Groby, Leicester, U.K.), was passed to within 1 cm of the aortic valve to measure systemic arterial pressure and obtain arterial blood samples. A left thoracotomy was performed and the fifth and sixth ribs excised. The pericardium was opened and the heart isolated and suspended in a pericardial cradle. The aortic fat pad was removed, the proximal aortic root dissected free, and an appropriately sized electromagnetic flow transducer (Transflow 601, Skalar Medical, Delft, Holland), attached to a flowmeter (S.E.M. 275, S.E. Medics, Feltham, U.K.), placed to measure aortic flow. A second rigid 8-French gauge cannula was inserted into the left ventricle, via a stab wound in the apical dimple, and attached to another pressure transducer for measurement of left ventricular pressure. A flexible catheter was inserted into the pulmonary artery via the right ventricular outflow tract for measurement of cardiac output by dye dilution. A segment of the descending thoracic aorta was isolated, and a length of surgical tape placed around the aorta to enable manual aortic constrictions to be made.

A segment of left anterior descending coronary artery (LAD) distal to the first diagonal branch was dissected free from the epicardium for placement of a 2-mm electromagnetic flow transducer. Distal to the flow probe, a snare was placed around the LAD and used for abrupt manual occlusions to obtain zero flow reference points.

Two pairs of piezoelectric crystals (5-MHz, 2-mm diameter) were placed in the subendocardium (in the minor axis of the left ventricle) to measure regional segmental length ultrasonically. One pair was located in an area supplied by the left anterior descending (LAD) coronary artery in the apical region, and the other in an area supplied by the left circumflex (LC) artery in the basal region.

After surgery was completed, anaesthesia with 1% halothane was continued for about 1 h, during which all transducers were calibrated. Halothane was then replaced by propofol which was administered as a bolus dose (5 mg kg^{-1}) over 5 min and after this as a constant infusion at a rate of 0.2 mg kg^{-1} min^{-1}. A 1-h period was allowed to elapse before recordings were made. A 10-s coronary occlusion and two 6-s aortic occlusions were performed. Blood samples were taken 10 min apart, before and after haemodynamic recordings, for measurement of blood concentrations of propofol. The infusion rate was changed to 0.4 mg kg^{-1} min^{-1} for 10 min and then reduced to 0.3 mg kg^{-1} min^{-1} for a 25-min equilibration period. After this period, a coronary occlusion and two aortic occlusions were performed. The procedure just described for the 0.3-mg kg^{-1} min^{-1} infusion rate was repeated for propofol infusion rates of 0.4 and 0.5 mg kg^{-1} min^{-1}, infusing at 0.5 and 0.6 mg kg^{-1} min^{-1} for the first 10 min, respectively. After the 0.5-mg kg^{-1} min^{-1} infusion, the rate was reduced to 0.2 mg kg^{-1} min^{-1} in order to test the extent of recovery. After a further 1-h equilibration period, coronary and aortic occlusions were carried out and blood samples were obtained. At the end of the experiment the dog was killed and coronary flow was calibrated by injection of 5-ml aliquots of heparinized blood through the coronary artery with the flow probe in place. The area supplied by the LAD artery was defined by injection of Evans blue dye into the vessel at the site of the flow transducer; careful weighing of the stained muscle allowed mean flow to be calibrated in ml min^{-1} per 100 g of muscle.

Mean arterial pressure was calculated from systolic and diastolic aortic pressures (SAP and DAP, respectively). The left ventricular pressure signal was fed to an analog differentiator to derive positive and negative LV dP/dt_{max}. Systemic vascular resistance (SVR) was calculated as the mean arterial pressure divided by the cardiac output. Coronary perfusion pressure (CPP) was calculated as the difference between the DAP and left ventricular end-diastolic pressure (LVEDP). Coronary vascular resistance was calculated by dividing CPP by coronary blood flow. Peak hyperaemic coronary flow was the greatest value for coronary flow after the 10-s occlusion periods. For normal load conditions, regional data were digitized manually. End-diastolic length (EDL) was measured at the time of the beginning of the sharp upslope of the first derivative of left ventricular pressure (LV dP/dt) signal. End-systolic length (ESL) was measured at the time the aortic flow first returned to zero. The end-systolic pressure–length relationship (ESPLR) was calculated for afterloaded beats. This involved measuring end-systolic pressures and the LAD and LC segment lengths for the first few beats following aortic occlusion. Linear regression analysis was carried out

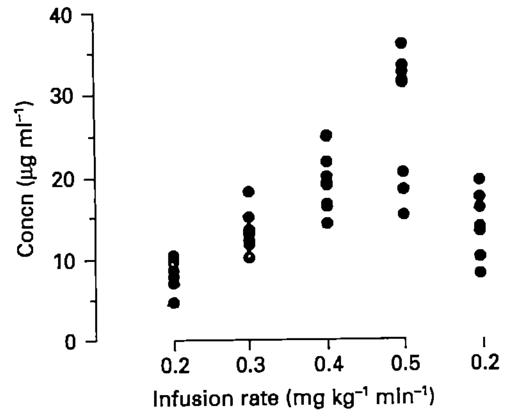

FIG. 1. Blood concentrations of propofol obtained with increasing infusion rates. Each point represents the mean of two measurements (10 min apart) during continuous infusion in eight dogs. At the 0.4- and 0.2- (recovery) mg kg^{-1} min^{-1} infusion rates, there are only seven propofol concentration data points.

upon the measured points using the least squares method. These calculations gave values for both the slope of the pressure–length relationship and the length axis intercept for both the LC and LAD regions for four different infusion rates of propofol. Percent systolic shortening (%SS) was expressed as a percentage of the EDL using the formula:

$$\%SS = [(EDL - ESL)/EDL] \times 100$$

Percent post-systolic shortening (%PSS) was calculated using the equation:

$$\%PSS = [(LminD - ESL)/(EDL - LminD)] \times 100$$

where LminD = minimum length during diastole.

Blood samples, taken at the time haemodynamic values were recorded, were analysed for propofol concentration by high pressure liquid chromatography with fluorescence detection [14].

For infusion rate dependent effects, the data were analysed using two-way analysis of variance and Duncan's multiple range test and analysis of variance for repeated measures. For drug concentration related effects, the data were subjected to linear regression analysis. $P < 0.05$ was considered significant. All values are given as mean (SD).

RESULTS

Blood concentrations of propofol obtained at increasing infusion rates are shown in figure 1 as individual values. Each point represents the average of the two blood samples taken at each of the five infusion rates. The samples were taken before and after haemodynamic recordings at the end of each infusion period (10 min apart). The mean percentage difference between paired samples was 19.5 (SD 16.7)%.The coefficient of variation of the assay over the same concentration range was 5–12%. Median propofol concentrations at the four increasing infusion rates were 8.25, 13.25, 18.9 and 31.45 µg ml^{-1}. Whereas there was an approximately linear relationship between drug input and measured concentrations at the three slowest infusion rates, the observed propofol concentration at 0.5 mg kg^{-1} min^{-1} was significantly different from the predicted value, and there was a wide range of values at this infusion rate (15.3–36.3 µg ml^{-1}). Because of this variability, we have analysed the data in two separate ways: with respect to infusion rate and with respect to individual drug concentration.

Global haemodynamics

The global haemodynamic data are shown in table I. Control values throughout were taken as those obtained with the initial 0.2-mg kg^{-1} min^{-1} infusion rate of propofol.

TABLE I. *Effect of increasing infusion rates of propofol on the circulation in eight dogs (mean (SD)). *P < 0.05 compared with the initial 0.2-mg kg⁻¹ min⁻¹ propofol infusion rate*

	Infusion rate of propofol (mg kg^{-1} min^{-1})				
	0.2	0.3	0.4	0.5	0.2
Heart rate (beat min^{-1})	129 (23)	119 (14)	115 (11)*	112 (7)*	116 (14)*
Systolic arterial pressure (mm Hg)	120 (17)	109 (10)	95 (11)*	81 (10)*	95 (15)*
Diastolic arterial pressure (mm Hg)	88 (15)	78 (11)	67 (12)*	51 (9)*	60 (12)*
LVEDP (mm Hg)	4.5 (1.9)	4.1 (1.9)	2.9 (1.4)*	3.1 (1)	3.4 (1.2)
LV (+)dP/dt_{max} (mm Hg s^{-1})	1863 (169)	1563 (302)*	1338 (220)*	1087 (247)*	1400 (346)*
LV (−)dP/dt_{max} (mm Hg s^{-1})	1838 (262)	1638 (177)	1412 (203)*	1137 (256)*	1528 (377)*
Cardiac output (litre min^{-1})	2.13 (0.6)	1.86 (0.54)	1.78 (0.58)*	1.48 (0.62)*	1.61 (0.46)*
Stroke volume (ml)	16.5 (3.5)	15.8 (4.5)	15.6 (5.3)	13 (5.1)*	14.8 (3.4)*
Systemic vascular resistance (dyn s cm^{-5})	4000 (1500)	4200 (1700)	3800 (1500)	3800 (1700)	3700 (800)
Aortic blood acceleration (ml s^{-2})	5653 (1390)	4728 (1836)*	4196 (1789)*	3138 (1452)*	3834 (1354)*
Coronary perfusion pressure (mm Hg)	83 (14)	74 (10)	64 (11)*	48 (9)*	57 (12)*
Coronary blood flow (ml min^{-1}/100 g)	36.3 (13.6)	30.8 (13.6)	24.7 (13.5)*	21.0 (16)*	24.9 (14.8)*
Peak hyperaemic flow (ml min^{-1}/100 g)	123.3 (46.9)	97.8 (38.5)*	73.9 (30.4)*	50.8 (24.9)*	58.9 (30.7)*
Coronary vascular resistance (mm Hg ml^{-1} min^{-1}/100 g)	2.8 (1.7)	3.0 (1.9)	3.5 (2.2)	3.3 (1.9)	2.9 (1.8)

TABLE II. *Effect of increasing infusion rates of propofol on regional haemodynamics in eight dogs (mean* (SD)). *$P < 0.05$ *compared with initial 0.2-mg* kg^{-1} min^{-1} *propofol infusion rate. The slopes of the LAD and LC regions differed significantly* ($P < 0.05$)

	Infusion rate of propofol (mg kg^{-1} min^{-1})				
	0.2	0.3	0.4	0.5	0.2
LAD					
EDL (mm)	11.70 (1.88)	11.56 (1.97)	11.29 (1.98)	10.98 (2.04)*	11.49 (1.78)
%SS	24.06 (7.02)	22.04 (7.33)	21.19 (7.14)*	19.11 (6.72)*	19.79 (5.87)*
%PSS	4.24 (7.85)	3.68 (10.4)	2.05 (4.1)	2.59 (7.31)	3.10 (6.66)
ES slope LAD (mm Hg mm^{-1})	107.6 (59.6)	100.9 (50.7)	79.6 (38.5)	56.1 (34.2)*	65.1 (37.2)*
Intercept LAD (mm)	7.84 (1.76)	8.15 (2.01)	7.88 (2.0)	7.51 (2.43)	7.91 (2.43)
LC					
EDL (mm)	13.49 (1.9)	13.33 (2.12)	13.1 (1.94)	12.41 (2.54)*	12.85 (2.05)
%SS	14.32 (6.92)	12.64 (3.73)	11.95 (3.79)	11.55 (2.34)	11.67 (2.67)
%PSS	12.64 (8.4)	13.31 (8.32)	14.62 (9.03)	12.12 (8.07)	11.61 (7.82)
ES slope LC (mm Hg mm^{-1})	96.7 (55.9)	88.4 (26.5)	72.3 (17.4)	51.1 (13.4)*	46.8 (16.9*)
Intercept LC (mm)	10.52 (1.95)	10.86 (2.06)	10.69 (2.01)	10.29 (1.77)	10.09 (1.69)

Increasing infusion rates of propofol decreased heart rate: 0.3-, 0.4- and 0.5-mg kg^{-1} min^{-1} infusion rates produced reductions in heart rate of 7.8%, 10.9% and 13.2%, respectively. These reductions were significantly different from control for the 0.4- and 0.5-mg kg^{-1} min^{-1} infusion rates. Both SAP and DAP were reduced by increasing propofol infusion rates; the reductions were statistically significant from control at 0.4 and 0.5 mg kg^{-1} min^{-1}. Infusion rates of 0.3, 0.4 and 0.5 mg kg^{-1} min^{-1} reduced SAP by 9.2%, 20.8% and 32.5%, respectively, and DAP by 11.4%, 23.9% and 42%, respectively.

LVEDP decreased with increasing propofol infusion rates, the difference reaching statistical significance with the 0.4-mg kg^{-1} min^{-1} infusion rate. LV dP/dt_{max} decreased significantly with increasing infusion rates of propofol: 0.3-, 0.4- and 0.5-mg kg^{-1} min^{-1} infusion rates reduced LV dP/dt_{max} by 15.8%, 32.6% and 42.1%, respectively. Further evidence that propofol depressed myocardial contractility was provided by the significant reductions in aortic blood acceleration produced with increasing infusion rates. Reductions of 16.4%, 25.8% and 44.5% occurred with infusion rates of 0.3, 0.4 and 0.5 mg kg^{-1} min^{-1}, respectively. Stroke volume (SV) also decreased with increasing infusion rates of propofol, although this reduction only reached statistical significance at the greatest rate of infusion of propofol, at which SV was reduced by 21.2%. As the reduction in SV was associated with a reduction in heart rate, cardiac output (CO) decreased with increasing infusion rates. These reductions were significant for the 0.4- and 0.5-mg kg^{-1} min^{-1} infusion rates (16.4% and 30.5%, respectively). Propofol significantly reduced the maximum rate of negative left ventricular pressure change ($-$LV dP/dt_{max}) with the 0.4- and 0.5-mg kg^{-1} min^{-1} infusion rates, by 23.2% and 38.1%, respectively. SVR was essentially unchanged by increasing propofol infusion rates.

During the recovery period at an infusion rate of 0.2 mg kg^{-1} min^{-1}, heart rate, SAP and DAP decreased significantly compared with the initial 0.2-mg kg^{-1} min^{-1} infusion rate—by 10.1%, 20.8% and 31.8%, respectively. Myocardial contractility and CO decreased also compared with control values (24.8% and 24.4%, respectively).

Coronary circulation

The coronary circulation data are shown in table I. Control values were taken as those obtained during the initial (0.2-mg kg^{-1} min^{-1}) propofol infusion.

CPP decreased significantly with increasing propofol infusion rates of 0.4 and 0.5 mg kg^{-1} min^{-1}: CPP was reduced by 22.9% and 42.2%, respectively, compared with control. Propofol significantly reduced coronary blood flow at the 0.4- and 0.5-mg kg^{-1} min^{-1} infusion rates compared with control values (by 32.0% and 42.1%). Maximal hyperaemic coronary blood flow (CBF_{max}) decreased significantly with increasing propofol concentration with the 0.3-, 0.4- and 0.5-mg kg^{-1} min^{-1} infusion rates, with which CBF_{max} was reduced by 20.7%, 40.1% and 58.8%, respectively.

Coronary vascular resistance did not change with increasing infusion rates of propofol.

Regional haemodynamics

Table II shows the effects of increasing infusion rates of propofol on mean EDL, %SS and %PSS. Control values are taken as those obtained during the initial (0.2-mg kg^{-1} min^{-1}) infusion of propofol.

Increasing rates of infusion of propofol decreased EDL. This decrease reached statistical significance with the 0.5-mg $kg^{-1}$$min^{-1}$ infusion rate: percent reductions, compared with control, were 6.2% and 8% for the LAD and LC regions, respectively.

The LAD region was found to have significantly decreased %SS compared with control for the 0.4- and 0.5-mg kg^{-1} min^{-1} infusion rates. In contrast, the decrease in %SS in the LC region was not significant. Differences in %SS between the LAD and LC regions were significant at all infusion rates, being greater in the LAD region than the LC region.

There was no apparent effect of increasing rates of infusion of propofol on %PSS.

Table II shows the effects of increasing rates of infusion of propofol on the slopes and length axis intercepts of the ESPLR for the LAD and LC regions. The greatest rate of infusion of propofol caused significant reductions in the slope of the ESPLR in both the LAD (-47.9%) and LC (-47.2%) regions. There was incomplete recovery in the LAD and further deterioration in the LC

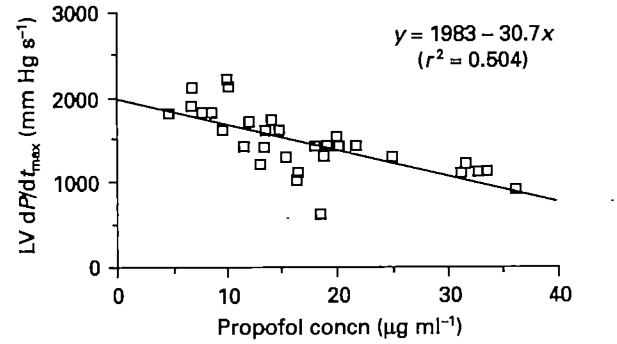

FIG. 2. Plot of LV dP/dt_{max} against blood concentration of propofol, showing the concentration-dependent effect of propofol on myocardial contractility. Each point represents the mean individual propofol concentration obtained during the four increasing infusion rates in each of eight dogs.

territory on returning to the 0.2-mg kg^{-1} min^{-1} infusion rate. The mean length axis intercept of the ESPLR for the LAD and LC regions did not change significantly with increasing propofol infusion rates.

The slopes of the ESPLR of the LAD and LC regions during the control (0.2-mg kg^{-1} min^{-1}) infusion of propofol were also found to differ significantly, the slope of the LAD region being steeper than that of the LC region. However, at greater infusion rates of propofol there were no significant differences between the slopes of the two regions.

Concentration-effect data

There were significant inverse correlations between SAP, DAP and propofol concentration (r^2 = 0.345 and 0.341, respectively). Similarly, positive (fig. 2) and negative LV dP/dt_{max} decreased with increasing concentrations ($r^2 = 0.504$ and 0.353, respectively), as did aortic blood acceleration (r^2 = 0.273). Both resting coronary blood flow and hyperaemic coronary flow decreased with increasing concentrations of propofol ($r^2 = 0.155$ and 0.380, respectively).

There were, however, no significant correlations between heart rate, LVEDP, SV, CO or SVR and blood concentrations of propofol. Similarly, at regional level, there was no significant correlation between %SS and blood concentration of propofol.

DISCUSSION

This study was designed to assess the effects on the circulation of increasing doses of propofol given by infusion. The slowest infusion rate of propofol used in this study (0.2 mg kg^{-1} min^{-1}) was the minimum rate compatible with anaesthesia in unstimulated, acutely instrumented dogs and has been used as the control rate in these investigations; the greatest infusion rate was 2.5 times that value.

Heart rate after administration of propofol has been reported as decreasing [1, 3, 15], increasing [16], or changing little [17]. In this study, increasing infusion rates of propofol resulted in a reduction in heart rate. Normally, arterial pressure is regulated by arterial baroreceptors which modify heart rate and systemic vascular resistance. Propofol appears to induce marked resetting of the heart rate baroreflex set point to allow slower heart rates despite decreases in arterial pressure; this is thought to be caused by increased vagal tone (or a sympatholytic effect, or both) [5]. A direct effect of propofol on the spontaneous rate of isolated atria, attributed to a reduction in Ca^{2+} fluxes has also been reported [18].

Arterial pressure was reduced by increasing infusion rates of propofol. This may be the result of reduced preload, depressed myocardial contractility or decreased systemic vascular resistance. High infusion rates of propofol resulted in decreases in EDL and LVEDP, which indicate a reduction in preload. This is consistent with observations by Goodchild and Serrao [9]. In addition, high infusion rates of propofol caused reductions in LV dP/dt_{max}, aortic blood acceleration and stroke volume, indicative of depressed contractility and global cardiac performance. However, there was no apparent effect of propofol on SVR. This is at variance with reports of decreases in SVR [2, 7, 9, 16], perhaps because of differences in methodology and basal vascular tone.

The maximal rate of pressure decline after end-ejection may be used as an index of ventricular relaxation [19]. A dose-dependent reduction indicates that propofol impaired ventricular relaxation. This may have been caused by a decrease in loading, as this is one of the determinants of relaxation. Another possible explanation is an effect of propofol on the inactivation process of cardiac contraction itself. This may result when calcium uptake into the sarcoplasmic reticulum is blocked, calcium leaks from these stores, the myocytes are unable to extrude the excess calcium, or when the affinity of the troponin for calcium is excessive. Indeed, it has been shown that propofol reduces calcium influx across the sarcolemma and the "tail" current that represents calcium-stimulated release of calcium from intracellular stores [10].

Although the coronary circulation is autoregulated, interventions which impair the function of smooth muscle in coronary vessels may attenuate local coronary flow regulation. In this study, regression analysis revealed a linear relationship between CPP and resting coronary blood flow (fig. 3). As propofol decreases myocardial oxygen demand, this indicates that propofol does not significantly affect coronary autoregulation.

Despite the dose range being only 2.5-fold, there was an 8-fold range in blood concentration of propofol. This reflects the kinetic variability seen in most studies in man and in experimental animals [13, 20]. Over this blood propofol concentration range (4.2–36.2 μg ml^{-1}), there were significant negative correlations between drug concentration and arterial pressure and left ventricular contractility. There was no concentration-related alteration in coronary vascular resistance, the reduction in coronary blood flow being a reflection of the reduced myocardial oxygen consumption associated with the reductions in systolic pressure and contractility. Increasing concentrations of propofol, however, resulted in attenuation of the hyperaemic response (fig. 3), that may be attributed to the reduction in CPP. The coronary vasodilator reserve, the difference between resting arterial coronary blood flow and flow measured during maximal vasodilatation

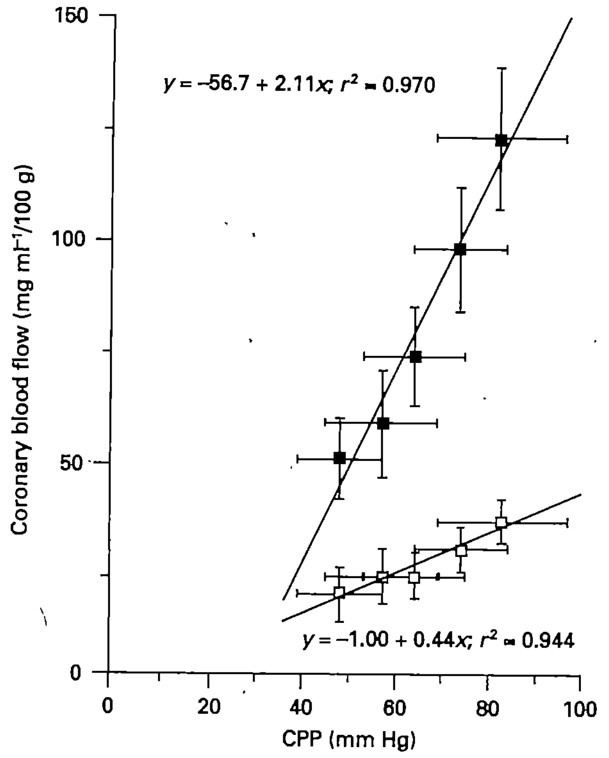

FIG. 3. Linear relationship between peak hyperaemic flow (■) and coronary perfusion pressure (CPP). The intercept of this relationship defines the critical closing pressure. ☐ = Relationship between resting coronary blood flow and coronary perfusion pressure. Each point represents mean (SD) from eight dogs.

(post-occlusion hyperaemia [21]), was reduced at greater concentrations of propofol, but was still 240 % of resting flow at the greatest rate of infusion of propofol.

Relationships between pressure and dimensions (ESPLR) are sensitive indices of myocardial contractility [22]. The ESPLR slopes were significantly reduced in both the apical and basal regions, implying depression of contractility in both regions. Analysis of mean slopes revealed that the apical region had a significantly greater contractile state throughout the dose–response study. This difference in contractility could be explained by a difference in sarcomere lengths. Indeed, Laks, Nisenson and Swan [23] demonstrated longer sarcomere lengths in the apex than in the base of the left ventricle. Longer sarcomere lengths would be expected to cause increased inotropy because of length-dependent changes in both myofilament Ca^{2+} sensitivity and the calcium transient during the contraction cycle [24]. The greater effect of propofol on the apex is not so easily explained, however. One possible explanation is that the greater sarcomere lengths in the apical region may afford a larger number of anaesthetic binding sites, as suggested by Diedericks, Leone and Foëx [25].

Regional differences were observed also in the values of %SS, the apex showing a statistically significant depression in the extent of %SS, while the base did not. Differences in wall tension may play a role in determining regional differences in %SS. As wall tension has been shown to be greater in the basal region than in the apical region [26], it could be anticipated that the basal region would shorten less but develop more tension during each contraction, while the apical region would develop less tension but shorten more.

In this study, the blood concentrations of propofol for a given infusion rate were greater than those reported by Naeije and colleagues [27] in closed-chest dogs. After the infusion rate of propofol had been returned to control values for the 1-h recovery period, blood concentrations of propofol were increased compared with those during the initial "control" propofol infusion rate (median 13.8 μg ml^{-1} *vs* 8.25 μg ml^{-1}). The smaller cardiac output during this recovery period may partially explain these alterations in propofol disposition (fig. 1). The depression of contractility after recovery was greater than that obtained during the 0.3-mg kg^{-1} min^{-1} infusion rate when blood concentrations of propofol were similar. These results suggest that, when myocardial depression has occurred following a prolonged infusion of propofol, increased blood concentrations of propofol, or both, recovery is delayed. Similar observations have been reported by Coetzee and colleagues [15] using an open-chested pig model.

While historical comparisons have to be considered with great caution, the effects of the greatest rate of infusion of propofol on mean arterial pressure were similar to those we have reported for 1.5 MAC of halothane, isoflurane and enflurane and the reductions in LV dP/dt_{max} were similar to those reported with 1 MAC halothane, 1.5 MAC isoflurane and 1.25 MAC enflurane [25, 28, 29]. Thus the greatest rate of infusion of propofol was associated with depression of cardiac function corresponding, at the most, to 1.5 MAC of inhalation anaesthetics, while this infusion rate was 2.5 times the minimum infusion rate necessary for the conduct of the study.

In conclusion, both reduced preload and depressed myocardial contractility contribute to the reduction in arterial pressure caused by propofol, systemic vascular resistance remaining unchanged. Increased rates of infusion of propofol also impaired relaxation. Autoregulation of coronary blood flow was maintained. Recovery was relatively slow after exposure to increased rates of infusion of propofol and may not parallel the anticipated decrease in anaesthetic concentrations.

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PORCINE MODEL FOR STUDYING THE PASSAGE OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKERS THROUGH THE BLOOD–BRAIN BARRIER

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SUMMARY

A method has been developed for blood–brain barrier disruption to provide reproducible access to the cerebrospinal fluid of the cerebellomedullary cistern. The technique was used successfully to investigate transfer of pancuronium to the cerebral CSF compartment in pigs. After osmotic disruption of the blood–brain barrier, pancuronium concentrations increased significantly in the cerebrospinal fluid.

KEY WORDS

Brain: blood–brain barrier. Cerebrospinal fluid: drug transfer. Neuromuscular relaxants: pancuronium.

It is accepted generally that quaternary compounds with a molecular centre carrying a strong positive charge do not cross the blood–brain barrier (BBB) in concentrations great enough to affect the brain. In spite of this, several neuromuscular blocking drugs have been shown to produce, not only EEG evidence of arousal reactions, but also decreases in frequency and amplitude in animals with disrupted BBB, which may indicate a depressant effect on the activating system of the medulla oblongata [1]. Therefore, interest has been focused on the passage of neuromuscular blockers through the supposedly compromised BBB and their possible toxic effects on cholinergic pathways in brainstem and midbrain structures [2]. If neuromuscular blocking agents do enter the CNS in large concentrations, recovery in patients with altered states of BBB might be delayed because of anticholinergic effects in midbrain structures (e.g. thalamus) [3].

There are few data on the passage of non-depolarizing neuromuscular blockers into the cerebrospinal fluid (CSF) in man [4, 5]. Furthermore, neither qualitative nor quantitative assessment of neuromuscular blocking drug penetration into the CSF before and after BBB disruption has been investigated under well controlled conditions.

The aim of this study was to develop a reliable technique for BBB disruption which also provides convenient access to the CSF of the cerebellomedullary cistern in the pig. After the model had been developed, we investigated the passage of pancuronium through the intact and disrupted BBB.

MATERIALS AND METHODS

Experimental procedure

After approval by the committee on animal research, we studied eight previously tested MH-free pigs (German breed) weighing 20–22 kg. Anaesthesia was induced by i.v. injection of thiopentone 10 mg kg^{-1} and maintained by a continuous infusion of 10–15 mg kg^{-1} h^{-1}. Additional opioids or inhalation agents were not administered. Tracheotomy was performed and ventilation using an oxygen–air mixture ($F_{I_{O_2}}$ 0.4) was adjusted to maintain arterial Pa_{CO_2} within normal limits (4.6–5.3 kPa) as assessed by capnography and intermittent blood-gas analysis. Ringer solution was infused i.v. at a rate of 3–5 ml kg^{-1} as required to keep haemodynamic variables within 10% of control values. In order to avoid excessive filling of the urinary bladder, suprapubic puncture and drainage was performed. An indwelling polyethylene catheter (0.9 mm i.d.) was placed in the right femoral artery for pressure recording and blood sampling. After exposure and ligation, the left common carotid artery (CCA) was cannulated (polyethylene cannula 1 mm i.d.), with the tip of the catheter just proximal to the occipital artery, for administration of hypertonic mannitol.

At first, the effects of continuous proximal CCA ligation on BBB integrity were investigated in three animals. After 60 min of CCA ligation, 2% Evan's blue 3 ml kg^{-1} was injected slowly via a peripheral vein for determination of BBB integrity. After an equilibration period of 10 min, the animal was killed with potassium chloride and the brain was removed immediately.

For cisternal catheter positioning, the animals were placed in a right lateral position with maximal flexion of the head to provide optimal access to the

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occipital bone. A midline incision was made from 3 cm proximal to approximately 13 cm distal to the external occipital protuberance. The muscles of the neck were separated by blunt dissection, the occipital bone exposed and the dorsal edge of the foramen magnum identified. The area between the nuchal ridge and the right atlanto–occipital junction was exposed. An 11-mm hole was drilled to give access to the dura mater; its position was selected exactly 1 cm cranial to the base of the occiput and approximately 1 cm medial to a vertical line through the right atlanto–occipital junction in order to avoid bleeding from extradural veins or from the median occipital sinus. After incision of the dura, cannulation of the cerebellomedullary cistern was performed by moving a polyethylene catheter (i.d. 0.5 mm, length 15 cm) along the dura approximately 2 cm in a medial and caudal direction. Correct position within the cisterna magna was confirmed by slow aspiration of clear CSF. Before insertion of the catheter, its tip was rounded by heating to avoid vascular lesions or damage of pial structures. Free flow of CSF was facilitated by two side holes within 5 mm of the tip. The drill hole was sealed with Histacryl to prevent both leakage of CSF and accidental removal of the catheter.

After completion of the surgical procedure and cisternal catheter placement, 25 % mannitol 3 ml kg^{-1} was injected slowly over 30 s into the left CCA to induce osmotic disruption of the BBB. The degree of BBB disruption was determined by assessing the staining of the cortex subsequent to injection of Evan's blue dye at the end of each experiment.

The staining of the brain was graded as follows: grade 0 = no staining; grade 1+ = just noticeable staining; grade 2+ = moderate blue staining; grade 3+ = dark blue staining [6, 7]. Correct catheter position in the cisterna magna was checked at autopsy.

Pancuronium assay in plasma and CSF

The concentration of pancuronium in CSF before and after mannitol-induced BBB disruption and plasma concentrations were measured by high pressure liquid chromatography [8]. Plasma and internal standard were mixed with potassium iodide–glycine buffer and dichlormethane for 30 s. After centrifugation, the bottom phase was evaporated to dryness at 45 °C under a stream of nitrogen. The dry residue was reconsisted in 250 µl of the HPLC eluent for further analysis. Liquor samples were analysed without extraction. A model 116 HPLC pump with a 210 A sample injection valve (Beckman Instr.) was used. The separation was carried out on a Nova Pak C18 column (Waters–Millipore) with a mobile phase consisting of sodium dihydrogen phosphate (NaH_2PO_4) 0.1 mol litre^{-1} (pH = 3.0, orthophosphoric acid (H_3PO_4) adjusted), 9,10-dimethoxy-anthracene-2-sulfonate (DAS) 0.11 mmol litre^{-1} heptansulfonate (HS) 0.11 mmol litre^{-1} in water–dioxane (85:15 v/v) at a flow rate of 1 ml min^{-1}.

For the purpose of the on-line post-column ion pair extraction, dichloroethane was added by a 880 PU-Jasco solvent delivery system and mixed with the HPLC eluent using a small deadspace volume T-piece. The extraction was performed in a 3.2-m × 1-mm i.d. coiled Teflon capillary connected to a sandwich-type phase separator. The phase separator consisted of a PTFE disc with a 42 × 1.5-mm groove sandwiched between two stainless-steel blocks. The split ratio of the phase separator was adjusted with a microcontrol needle valve BMVC (SGE) mounted in the outlet of the upper steel block.

The fluorimetric detector (LS-2B, Perkin Elmer) was set at 385 nm (excitation) and 452 nm (emission). After each series of analyses, the HPLC-column was flushed with water (approx. 15 ml) and methanol (approx. 75 ml). The HPLC-system was operated and the chromatograms were recorded and processed with System Gold chromatography software (Beckman Instr.).

Linearity was observed ($r = 0.9956$) over a range of 0.05–10 µg ml^{-1}. The extraction recovery was approximately 30–70 % compared with that of unextracted standard samples. The limit of detection for all substances (pancuronium and its metabolites) was approximately 5 ng ml^{-1}.

Pancuronium penetration into the cerebral CSF compartment before and after disruption of the blood–brain barrier

Having established the method in preliminary studies, we applied the technique in eight additional experiments.

After completion of the operative procedure, neuromuscular monitoring was commenced using supramaximal (2–4-mA) stimulation of the common peroneal nerve with stimuli of 0.2 ms duration at a rate of 0.1 Hz and anterior tibial muscle mechanomyography. After a stabilization period of 10 min, a bolus dose of pancuronium 220 µg kg^{-1} ($2 \times ED_{90}$) was given i.v. and, after spontaneous twitch recovery to 10 % of control, an infusion of pancuronium was administered continuously for 60 min; the infusion rate was adjusted to keep neuromuscular block at 85–90 % of control. Blood and CSF samples were obtained 2, 10, 30, 60 and 90 min after the administration of the bolus dose of pancuronium.

After complete spontaneous recovery of neuromuscular function, each animal was given 25 % mannitol 3 ml kg^{-1} to disrupt the BBB, and the animal was subjected again to the programme as described above.

At the end of the experiment, Evan's blue was injected i.v.; 10 min later the animal was killed and the brain removed immediately for assessment of the level of brain staining as evidence for BBB disruption.

Statistics

Pancuronium concentrations in plasma and CSF were assessed statistically using the Wilcoxon test for paired data. Level of significance was assumed to be 95 % ($P < 0.05$). Data are presented as mean values (SEM).

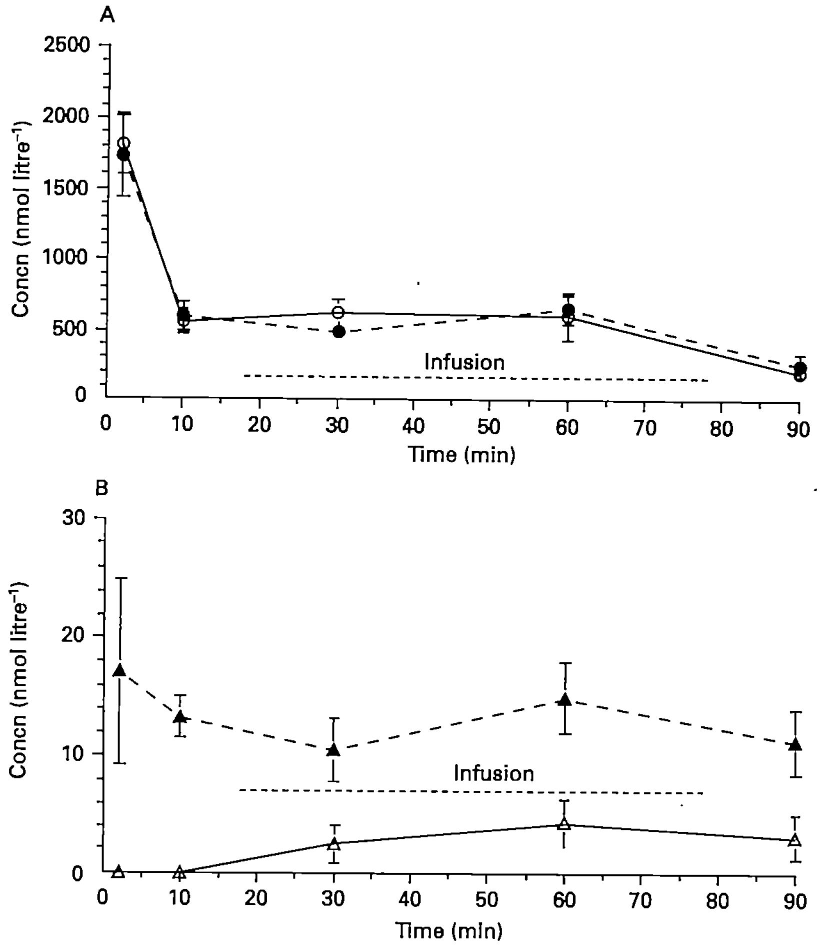

FIG. 1. Time course of mean (SEM) plasma (A) and CSF concentrations (B) of pancuronium before (○, △) and after (●, ▲) osmotic disruption of the BBB. At 0 a 2 × ED$_{90}$ bolus dose was administered; continuous infusion from 18 to 78 min. Pancuronium concentrations in the CSF after BBB disruption were significantly greater ($P < 0.05$).

RESULTS

Haemodynamic and respiratory variables remained stable throughout all experiments.

Unilateral common carotid artery ligation

Unilateral common carotid artery ligation produced no haemodynamic effects. In the three animals subjected to this procedure, Evan's blue staining was not detected 60 min after continuous ligation of the CCA.

Access to cerebrospinal fluid

Using the transoccipital approach, clear CSF could be obtained in each case as required by the study. Correct catheter position within the centre of the cerebellomedullary cistern was confirmed at autopsy.

Osmotic blood–brain barrier disruption

In all cases, reproducible Evan's blue staining of the cortex (grade 2+ = moderate blue staining) was obtained, which suggests that the desired degree of BBB disruption was achieved with 25% mannitol 3 ml kg^{-1} injected into the CCA.

Concentration of pancuronium in the cerebrospinal fluid before and after disruption of the blood–brain barrier

There was no statistically significant difference in plasma concentrations of pancuronium before and after BBB disruption (fig. 1A). In contrast, after osmotic disruption of the BBB a significantly greater concentration of pancuronium was detected in CSF (fig. 1B). The CSF:plasma ratio was 0.023, which is significantly greater than the ratio of 0.005 before disruption of the BBB.

DISCUSSION

Osmotic disruption of the BBB by direct or retrograde infusion of hypertonic solutions into the internal carotid artery has been standardized in small rodents, monkeys and dogs [6, 9, 10]. In the pig, as a result of certain anatomical differences in arterial blood supply of the brain, only the CCA is accessible for injection of hypertonic solutions. When this approach is used for BBB disruption, continuous CCA ligation may result, not only in BBB breakdown, but also in an increased incidence of apnoea, bradycardia, hypotension or even permanent brain damage [11]. However, our preliminary studies clearly showed that unilateral continuous CCA ligation in the pig was not followed by undesired haemodynamic responses and in no case was Evan's blue staining detected in brain, even after a 60-min period of continuous ligation. This demonstrates that, in the pig, sufficient collateral cerebral circulation is provided by the dense extradural arterial network which is supplied by both CCA [12].

In earlier studies the injection of hypertonic mannitol 1.5 ml kg^{-1} into the CCA in dogs resulted in inconsistent BBB disruption because of a large distal external to internal carotid collateral circulation via the snout [10, 13]. Taking into account the apparently larger capacity of the complex cerebro–arterial system in the pig, in the present study 25% mannitol 3 ml kg^{-1} was used to produce the desired degree of disruption. In all experiments this was followed by a moderate Evan's blue staining of both hemispheres, indicating osmotic breakdown.

Even minimal blood staining of CSF impedes reliable qualitative and quantitative assessment of drug transfer through the BBB. Although several methods of access to the cerebral ventricular system and the subarachnoid space of the cerebellomedullary cistern have already been described in the pig, frequent withdrawal of clear (not blood-stained) CSF could not be guaranteed [14, 15]. When stereotaxic insertion of the ventricular cannula is used, CSF removal is frequently unsuccessful because of ventricular collapse or blocking of the cannula by the choroid plexus. In addition, stretching and distortion of choroid vessels by suction may cause progressive bleeding and may consequently lead to unintended mechanical damage of the BBB. In the cerebellomedullary cistern, the subarachnoid space is rather small and the distance between the atlanto–occipital membrane and the medulla oblongata is usually < 5 mm in pigs weighing 20–22 kg. Thus a percutaneous technique with subsequent puncture of the atlanto–occipital membrane may not permit correct catheter positioning. A misplaced catheter may result immediately in a dry tap, disastrous puncture of the medulla oblongata or blood-stained CSF as a result of damage to pial vessels. In order to guarantee reliable access to clear CSF, a retrograde approach to the cerebellomedullary cistern has been developed and used successfully in our experiments. Meticulous placement of the occipital drill hole within the described anatomical structures and careful movement of the catheter in a medio–caudal direction has proved to be of the utmost importance.

When studying the passage of any drug through the BBB over a given period, it is essential that the amount of CSF withdrawn for analysis does not exceed its rate of production. There are no data available for the rate of CSF formation in the pig, but, assuming the rate is comparable to that in the dog, withdrawal of 0.3–0.5 ml every 10 min is reasonable [16].

The animal model described has been used successfully to study the passage of pancuronium from blood to CSF. Despite being ionized, i.v. administered pancuronium passes into the CSF in small amounts, the resulting CSF : plasma ratio being very small. However, after BBB disruption a significantly greater concentration of pancuronium was detected in CSF.

In conclusion, the pig serves as an excellent model for investigating the passage of drugs through the intact and disrupted BBB. The data obtained from this experimental model strongly suggest that i.v. administered pancuronium might yield CSF concentrations large enough to affect the CNS when the BBB is compromised. This should be considered whenever neuromuscular blocking agents or other drugs not thought to cross the BBB are administered simultaneously with high-dose mannitol, for example to enforce diuresis or to reduce rapidly an increased intracranial pressure.

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REVIEW ARTICLE

ONE-COMPARTMENT KINETICS

J. NORMAN

Pharmacokinetics may appear daunting, especially if the background mathematical development is presented too briefly and if the number of compartments or subdivisions of the model are too many. The aim of this review is to develop the basic model and concepts with a more rigorous mathematical treatment. The review is confined to considerations of a single compartment, but even such a simple model has its uses in conditions in which the distinction between "fast" and "slow" components is not all that significant. The model is built up to show what happens with bolus injections, with infusions, with combinations and also with a decreasing rate of input such as may be seen after an i.m. injection.

The initial section gives a revision of the mathematics involved and the next is the development of the necessary equations to accompany the model. These are applied to the use of a drug such as morphine for the control of pain in the first 24 h after operation. These illustrations have been chosen to show what can happen with several common techniques.

MATHEMATICAL REVISION

The concept of a function

In the model, several equations are developed which are examples of *functions*. A function is, simply, a *rule* by which an independent variable (usually symbolized by x or t) may be transformed uniquely into a dependent variable (the y value). Thus

$$y = 2x^2$$

is a function. The rule is that for a given value of x, y is given by squaring x and doubling that answer. Similarly,

$$y = x^3 + 2x + 1$$

is a somewhat more complex function but, again, for any x value a corresponding value for y is calculated by the rules given in the equation. A more general expression would be:

$$y = f(x)$$

where x = the independent value and y the result of applying the rule summarized by $f(x)$. Other general expressions for a function may include:

$$y = g(x)$$

All the symbols imply is that, for a set of values of a dependent variable, there is some rule symbolized by $f(x)$ or $g(x)$ which allows us to calculate the independent variable.

Exponential functions

The two equations given above use powers of x—that is, both expect that (in part) x has to be multiplied by itself once or more often. With exponential functions, the difference from power functions is that the independent variable is the power. We shall be developing several such functions where a particular constant (e) is raised to the power of the independent variable. e is an irrational number the value of which is approximately 2.71828... and may be calculated with any desired degree of accuracy from the binomial expansion of:

$$e = (1 + 1/n)^n$$

as n approaches infinity. For $n = 1$ the value is 2; for $n = 10$ the value is 2.594; for $n = 100$ it is 2.705 and for $n = 1000000$ it is 2.71828.

The value of e may also be calculated from the expansion of the series:

$$e = 1 + \frac{1}{1} + \frac{1}{1.2} + \frac{1}{1.2.3} + \frac{1}{1.2.3.4} + \ldots$$

An exponential function may resemble a function such as:

$$y = e^x$$

or

$$y = e^{f(x)}$$

for there is no reason why we cannot use a function of x as the exponent; indeed we usually shall. The series giving e^x is given by:

$$e^x = 1 + \frac{x}{1} + \frac{x^2}{1.2} + \frac{x^3}{1.2.3} + \ldots\ldots$$

Differentiation

With pharmacokinetics we are often interested in rates of change—how quickly a blood concentration decreases after an i.v. injection or how quickly it increases during an i.v. infusion. Further, we can usually calculate how quickly a dependent variable (the concentration) changes and we shall want from that estimate to be able to calculate what the actual value may be at any one instant.

Rates of change are thus of vital interest. They

KEY WORDS

Pharmacokinetics: single compartment model. Analgesics: morphine.

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form the basis of *differential calculus*. There are several rules which we must remember in order to build up kinetic models.

Rule 1. If the function is

$$y = x^n$$

then the rate of change (symbolized by dy/dx) is:

$$dy/dx = n.x^{n-1}$$

The proof of this is developed easily and is found in any standard textbook (e.g. [5]).

Rule 2. If the function is:

$$y = x^n + C$$

where C = an arbitrary constant, the rate of change of y with x is uninfluenced by C and is given by:

$$dy/dx = n.x^{n-1}$$

Rule 3. If the function is:

$$y = A.x^n + C$$

where A = another constant, the rate of change is given by:

$$dy/dx = n.A.x^{n-1}$$

Rule 4. If the function is a sum of sub-functions such as

$$y = A.x^n + B.x^m + C$$

the rate of change (or derivative) is the sum of the two derivatives, that is:

$$dy/dx = n.A.x^{n-1} + m.B.x^{m-1}$$

Rule 5. (The chain rule). Suppose there is a function of a function: thus if

$$z = f(y) \text{ and } y = g(x)$$

where $g(x)$ represents a second function, then the rate of change of z with respect to x is given by

$$dz/dx = dz/dy * dy/dx$$

Exponential differentiation

The rules given above may be applied to exponential functions. The unique character of an exponential function is shown by differentiating:

$$y = e^x$$

The series giving e^x was given above:

$$e^x = 1 + \frac{x}{1} + \frac{x^2}{1.2} + \frac{x^3}{1.2.3} + \ldots\ldots$$

Using the rules given above:

$$\frac{dy}{dx} = 0 + 1 + 2\frac{x}{1.2} + 3\frac{x^2}{1.2.3} \ldots$$

or

$$e^x = 1 + \frac{x}{1} + \frac{x^2}{1.2} + \frac{x^3}{1.2.3} + \ldots$$

that is

$$dy/dx = e^x$$

Thus the rate of change of this exponential function is the same as the function itself. For other more complex exponential functions the other rules may be applied. For example, if

$$y = A.e^x$$

then

$$\frac{dy}{dx} = A\frac{de^x}{dx} = A.e^x$$

What happens when the exponent is a multiple of the independent variable? The chain rule applies. Suppose

$$Y = A.e^{\alpha x}$$

This function may be looked at as being composed of the product of two parts. If we let

$$z = \alpha.x$$

then

$$Y = A.e^z$$

The two differential equations are:

$$\frac{dz}{dx} = \alpha$$

and

$$\frac{dy}{dz} = A.e^z$$

Multiplying the two together gives:

$$\frac{dy}{dx} = \frac{dz}{dx}\frac{dy}{dz} = \alpha A.e^{\alpha x}$$

This equation is of fundamental importance for kinetic understanding. If the coefficient α is positive, the process is of exponential growth and the rate of growth at any one time is proportional to the actual value at that time. If α is negative, the process is of exponential decay, where the rate of decay at any one time is again proportional to the actual value at that time. We shall meet many examples of such exponential decay in pharmacokinetics. Decay constants are often expressed in another form—as half-lives. The relationship between half-life and the decay constant (commonly given the symbol β) is given by:

$$T_{\frac{1}{2}} = \frac{\ln(2)}{\beta}$$

Differential equations

With pharmacokinetic models it is often relatively easy to write an equation giving the rate of change of concentration of the drug; what is more difficult is to solve that equation so as to calculate what the concentration of drug is at any given time. Generally, in solving such equations, we need to have some additional information to give a known concentration at a particular time. (An easier example to think of may be that any given straight line is given by knowing its intercept on the y axis and the value for the slope. Many lines have the same slope and only when the intercept is known or can be calculated may we identify a specific line. The same is true for differential equations.) That information, together with the differential equation, leads to a solution of the problem.

Most standard pharmacokinetic texts give the solutions for several input conditions such as a bolus injection or a constant infusion. Such solutions may be checked by differentiating the solution to ensure that the differential matches the theoretical prediction. An alternative approach is to develop a method of producing a more direct solution. With the differential equations in use here, the method involved is to use a Laplace transform (see Appendix, including table I). This mathematical device allows us to remove terms such as dy/dx or dC/dt, where C represents concentration, and replace them with others which can be manipulated algebraically. When an expression is finally derived, it may be converted back into concentration terms by using the inverse transform. Whilst developing the transform is difficult, there are "cook-book" recipes (e.g. [4]) which make the task easier.

The use of both approaches is described here.

THE ONE-COMPARTMENT MODEL

The aim of this section is to develop the necessary differential equations and their solutions to allow us to calculate what the concentration of drug (morphine) is after a bolus injection, a constant infusion or a combination of the two, when we regard the body as composed of a single compartment. In addition, we shall develop the equations to describe what happens in a situation similar to that occurring after an i.m. or s.c. injection, when all the drug appears eventually in the circulation. Figure 1 shows the basic model. The symbols used are those adopted by the *British Journal of Anaesthesia* in accordance with the proposal of Hull [2].

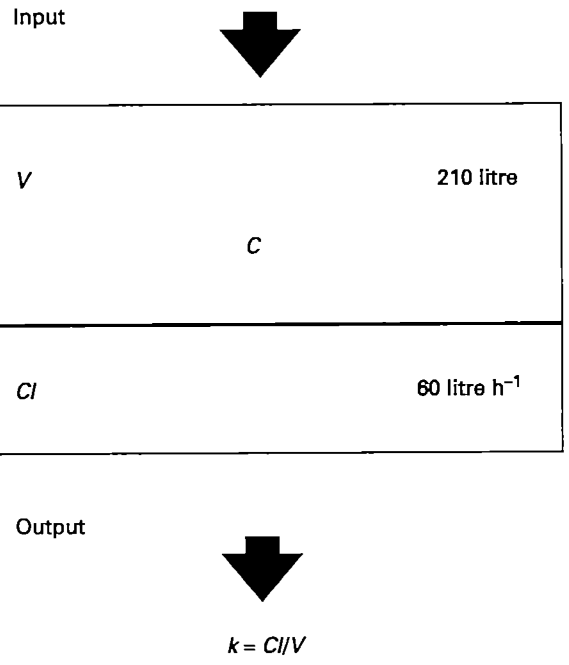

FIG. 1. The one-compartment model. The compartment is represented by the area of the box corresponding to the volume (V) with the lower part identified as the fraction of the volume cleared in unit time (Cl). The drug is *input* into the model as an instantaneous bolus, a constant rate i.v. infusion, or a combination of these, or may leak into the compartment exponentially from another source (the "i.m." injection). The drug is cleared from the compartment at a rate (k) determined by the ratio of the clearance to the volume.

Assumptions

In order to derive the equations, there are several assumptions that must be made to simplify the arithmetic.

1st assumption. Any drug within the compartment is mixed instantaneously throughout the compartment. Thus at any time, if we know the *volume* (V) of the compartment and the total *amount* or quantity of drug within the compartment (X) at a given time, t, then the concentration of drug at that time (C) is given by:

$$C=\frac{X}{V} \tag{1}$$

2nd assumption. The volume (V) remains constant during the period under study.

3rd assumption. The rate at which drug is removed from the compartment is proportional to the amount present. This frequently applies, especially to such processes in which the drug is removed by filtration or where it is metabolized with a large concentration of enzyme being present.

Thus, in general, over a small interval of time (Δt):

$$Xd_{out} = -\Delta t.k.Xd$$

where Xd_{out} = amount being eliminated, k = a constant and Xd = amount of drug present. The differential equation showing the rate of change of amount present is:

$$dX_{out}/d_t = -k$$

Given assumption 2, that the volume remains the same, we can also write the equation in concentration terms (C):

$$dC_{out}/dt = -k/V$$

Clearance. The clearance (Cl) of a drug is best described formally as the rate at which drug is eliminated (dX_{out}/dt) per unit concentration of the drug (C). Thus:

$$Cl = (dX_{out}/dt)/C$$

In terms of units, the rate of removal may be expressed in units of mass of substance per unit of time and the concentration in terms of mass of substance per unit of volume. The effect is that clearances are expressed in units of volume per unit time.

This last equation may be modified further from a knowledge of the relationship between amount of drug present and the volume. Thus:

$$Cl=\frac{\frac{dX_{out}}{dt}}{\frac{X}{V}}$$

or, by rearrangement:

$$\frac{dX_{out}}{dt}=\frac{Cl}{V}X$$

Thus, if the volume (assumption 2) and the clearance remain constant, the drug is removed exponentially. The ratio of the clearance to the volume is the rate constant for elimination—that is:

$$k = Cl : V$$

In general, we can control the input of drugs into the patient, but elimination depends on filtration or metabolism, or both, and is less easy to manipulate. If the rates of filtration or metabolism are proportional to the amounts (or concentrations) of drug present, we can write the following for the amount of drug removed over any short interval of time (Δt):

$$\Delta X_{\mathrm{out}} = -\Delta t . Cl . C$$

or, in terms of concentrations:

$$\Delta C = -\Delta t . Cl . C . \frac{1}{V}$$

As we let the time interval become infinitesimally small, we can write the differential equation thus:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = -\frac{Cl}{V} \times C$$

In order to find what concentration exists at any time, we must solve this differential equation. Most textbooks give the solution without proof. The solution (what concentration exists at any given time, t (C)) is:

$$C = C^0 \mathrm{e}^{-\frac{Cl}{V}t} \qquad (2)$$

where C^0 = concentration at the start of elimination (at time zero). The equation can be checked by differentiating it and using equation (2) in substitution:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = -\frac{Cl}{V} \times C^0 \mathrm{e}^{-\frac{Cl}{V}} = -\frac{Cl}{V} \times C$$

The alternative development is to use the Laplace transform. In essence, this transformation looks at the differential equation and, where we find the dependent variable (C) or its derivative, these are replaced by appropriate functions of a new variable (s). The relevant rules for making these changes are summarized in the Appendix.

First, we rearrange equation (2) to:

$$\frac{\mathrm{d}C}{\mathrm{d}t} - \frac{Cl}{V} C = 0$$

Any term involving only the dependent variable (or a constant multiplying the variable) is transformed to be a new function ($g(s)$). Any term involving a derivative of the dependent variable is transformed into an expression of the following form:

Change $\mathrm{d}C/\mathrm{d}t$ into $s.g(s) - C^0$

where s = the Laplace operator, $g(s)$ = the new function of that operator and C^0 = the concentration present at the start of the process. The whole transformed equation becomes:

$$s.g(s) - C^0 - \frac{Cl}{V}.g(s) = 0$$

This, in turn, can be rearranged:

$$g(s)\left(s - \frac{Cl}{V}\right) = C^0$$

or

$$g(s) = \frac{C^0}{\left(s - \frac{Cl}{V}\right)}$$

This equation can now be transformed back to one giving the concentration at any given time (C). The table in the Appendix shows that the inverse transform of an expression of the form $(1/(s-a))$, where a is a constant, is given by the expression e^{-at}. The new term a is given by Cl/V when we transform back. The constant C^0 remains unchanged. Thus we return to the solution given above:

$$C = C^0 . \mathrm{e}^{-\frac{Cl}{V}t} \qquad (2)$$

Bolus injection into the single compartment

This equation describes well what happens when all input into the model has ceased or, more readily, what happens after a bolus injection into the empty model. In the latter event, the initial concentration (C^0) is given by dividing the dose injected (Xd) by the volume (V). Remember that the first assumption is that any drug is mixed instantaneously in the volume. Thus the solution for a bolus injection into the model which was previously empty becomes:

$$C = \frac{X\mathrm{d}}{V} \mathrm{e}^{-\frac{Cl}{V}t} \qquad (3)$$

As an example, consider what happens when we give an i.v. dose of morphine (say 10 mg) to a patient. Assume the one-compartment model is valid and that for the average 70-kg adult the volume of distribution is 210 litre and the clearance about 60 litre h^{-1}. The equation giving the concentration at any time after the injection thus becomes (in units of µg litre^{-1}):

$$C = \frac{10000}{210} \mathrm{e}^{-\frac{60}{210}t}$$

Figure 2 shows the graph of the resulting exponential decay.

If the therapeutic plasma concentration of morphine for the control of postoperative pain is in the range 25–50 µg litre^{-1}, then this injection should produce relief for about 2 h.

Constant infusion into the single compartment

With this variant, we need to consider in more detail the input and the output from the model. The output, as before, is given by:

$$\Delta X_{\mathrm{out}} = -\Delta t . Cl . C$$

The input is given by multiplying the infusion rate (k') by the time interval (Δt):

$$\Delta X_{\mathrm{in}} = \Delta t . k'$$

and the net change is:

$$\Delta X = \Delta t(k' - Cl . C)$$

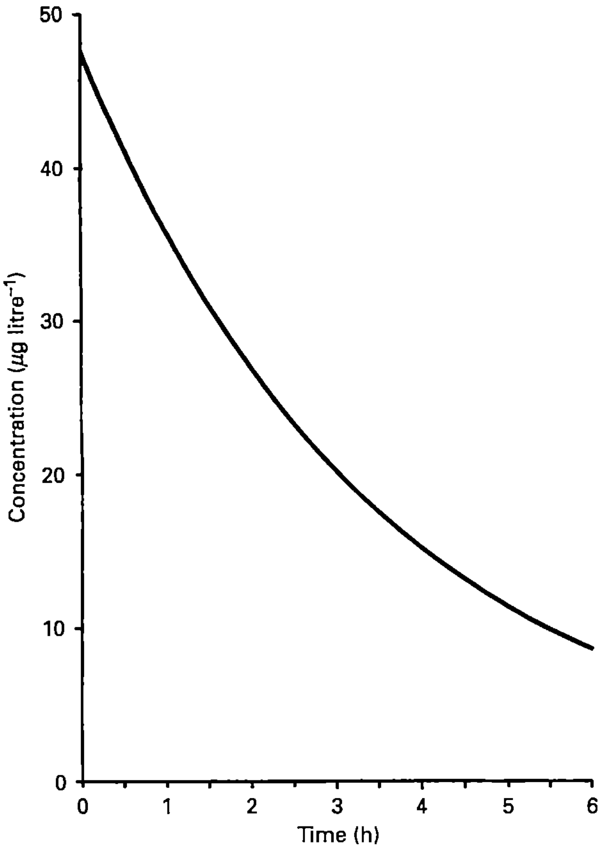

FIG. 2. Hypothetical example of the concentration of morphine in a one-compartment model when 10 mg is given as an initial bolus into a volume of 210 litre and with a clearance of 60 litre h^{-1}.

In terms of changes in concentration, the equation changes to:

$$\Delta C = \frac{1}{V}(k' - Cl.C)\Delta t$$

and, in the limit as Δt becomes infinitely small, we can write:

$$\frac{dC}{dt} = \frac{k'}{V} - \frac{Cl}{V}.C$$

Rearrange this to get all the terms involving concentrations and rates of change on one side:

$$\frac{dC}{dt}V + Cl.C = k'$$

The Laplace transforms for the terms on the left have been given already. The transform for the constant (k') on the right hand side is given by k'/s. The transformed equation is:

$$V(s(g(s) - C^0)) + Cl.g(s) = \frac{k'}{s}$$

This is solved for $g(s)$—the transformed function of the concentration:

$$g(s)(V.s + Cl) = V.C^0 + \frac{k'}{s}$$

or

$$g(s) = \frac{V.C^0}{V.s + Cl} + \frac{k'}{s(V.s + Cl)}$$

Divide the top and bottom of the terms on the right hand side by V to simplify the result:

$$g(s) = \frac{C^0}{\left(s + \frac{Cl}{V}\right)} + \frac{\frac{k'}{V}}{s\left(s + \frac{Cl}{V}\right)}$$

The inverse transform of the first term has already been given (see equation (2)). That for the second term is shown in table I in the Appendix. The inverted equation thus becomes:

$$C = C^0 e^{-\frac{Cl}{V}t} + \frac{k'.V}{V.Cl}(1 - e^{-\frac{Cl}{V}t})$$

This simplifies to:

$$C = C^0 e^{-\frac{Cl}{V}t} + \frac{k'}{Cl}(1 - e^{-\frac{Cl}{V}t}) \qquad (4)$$

For a constant rate infusion when there is no drug present initially, the first term on the right hand side must be zero and the equation simplifies to:

$$C = \frac{k'}{Cl}(1 - e^{-\frac{Cl}{V}t}) \qquad (5)$$

If we look at this in more detail, at time zero before the infusion starts the expression $e^{-0} = 1$ (by definition) and the equation evaluates the concentration as being zero. At infinity, $e^{-\infty}$ evaluates as 0 and the equation gives the final concentration as being given by the ratio of the infusion rate (in mass units per unit time) divided by the clearance (volume divided by time). This makes sense, given the definition of clearance—the rate of drug removal per unit concentration. Alternatively, if we know what steady state concentration we want, we can calculate the infusion rate:

$$k' = C^{ss}.Cl \qquad (6)$$

Infusions of morphine are now being used more commonly to reach a more steady state in terms of pain control. Figure 3 shows the pattern of drug concentration seen with this model with an infusion of 2.5 mg h^{-1}, given the same parameters as for figure 2. The concentration climbs almost to a plateau of approximately 40 µg litre^{-1} by about 10 h. Remembering that the elimination half-life is given by multiplying the natural logarithm of 2 by the ratio of the clearance divided by the volume of distribution (about 2.43 h for this example) we can see that it takes four to five half-lives to reach this point. If analgesia were obtained only when the concentration reached 25 µg litre^{-1}, then that would take about 3 h.

Combining a bolus dose and an infusion

Equation (4) has other uses for our model. The second term gives the concentration produced by the infusion. The first term gives the decay in concentration that occurs for any drug already in the system. So far we have assumed the compartment is empty at the start. What happens if, at the start of the infusion, we also give a bolus dose (d) in an amount

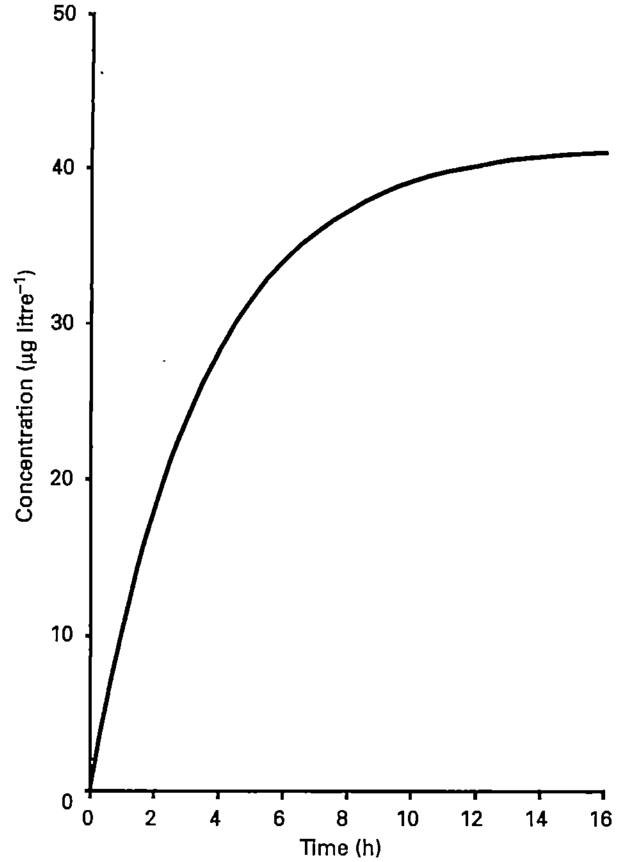

FIG. 3. The one-compartment model of the morphine concentration to be achieved with a constant rate infusion of 2.5 mg h^{-1}. The volume and clearance are the same as in figure 1. The half-life is 2.43 h. By 10 h, the infusion is producing a reasonably steady state—that is, after about four half-lives.

*X*d? Obviously, the initial concentration then becomes *X*d divided by the volume:

$$C^0 = Xd/V$$

and, for any subsequent time during the infusion:

$$C = \frac{Xd}{V}e^{-\frac{Cl}{V}t} + \frac{k'}{Cl}(1 - e^{-\frac{Cl}{V}t}) \qquad (7)$$

This can itself be simplified to:

$$C = \left(\frac{Xd}{V} - \frac{k'}{Cl}\right)e^{-\frac{Cl}{V}t} + \frac{k'}{Cl} \qquad (8)$$

This equation is worth examining in more detail. The last term on the right gives the steady state concentration achieved with the infusion. The first term is composed of two parts: the initial one giving the effect of the bolus dose and its decay, and the next the decay from the infusion. Thus we can see that we are adding the two decay processes together.

Giving a bolus injection at the start of an infusion is an effective way of achieving the concentration we need rapidly and then maintaining it. To get a given steady state concentration (C^{ss}) we need to know the size of the bolus dose and this must be given by multiplying the volume of distribution by the desired concentration, thus:

$$Xd = V*C^{ss}$$

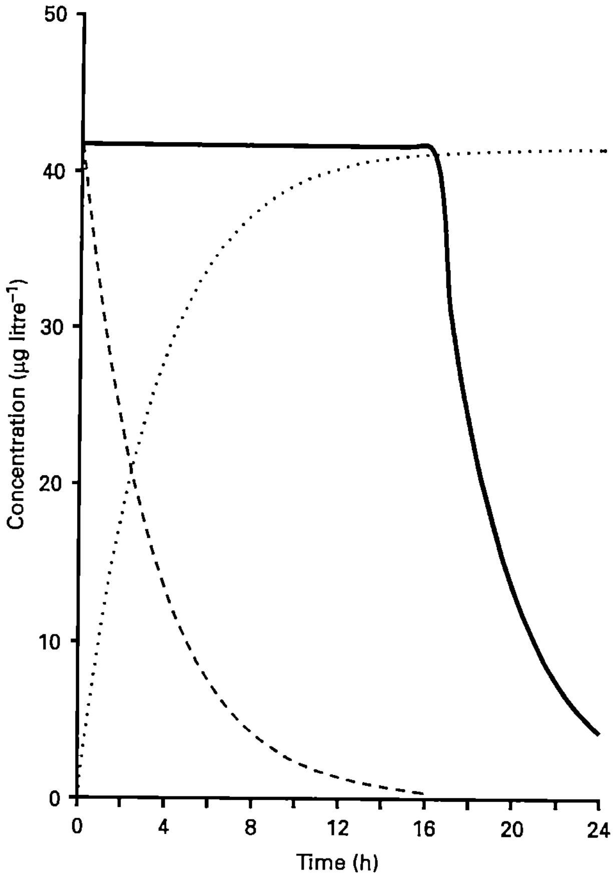

FIG. 4. The effects of combining an infusion (2.5 mg h^{-1}) with a bolus dose (8.75 mg) given at the start of the infusion. – – – = Concentration profile for the bolus; · · · · = concentration profile for the infusion; —— = concentration profile for the combination. Stopping the infusion at 16 h leads to an exponential decay, as with the bolus alone.

The infusion rate, similarly (as before), is given by the product of the clearance and the concentration:

$$k' = Cl*C^{ss}$$

Substituting C^{ss} for the appropriate terms in equation (7) we derive:

$$C = C^{ss}e^{-\frac{Cl}{V}t} + C^{ss}(1 - e^{-\frac{Cl}{V}t})$$

or

$$C = C^{ss}$$

Figure 4 shows how this approach would work for morphine. Suppose the target concentration were 40 µg litre^{-1}. The infusion rate can be calculated as 2.5 mg h^{-1} and the bolus dose 8.75 mg. Figure 4 shows the two components and the sum and, also, the decay to be seen when the infusion is finished after about 16 h.

There is one other modification which enlarges the range of uses of equation (7). We often want to know what happens if, after giving a bolus or infusion or combination, we give another bolus or change the rate of infusion. We must calculate the residual concentration at the times when the changes are made. This becomes the concentration (C^0) at the new start time. Changing the infusion rate gives a new value for *k*′. Giving a bolus dose changes the value of C^0 by adding to it the increase in

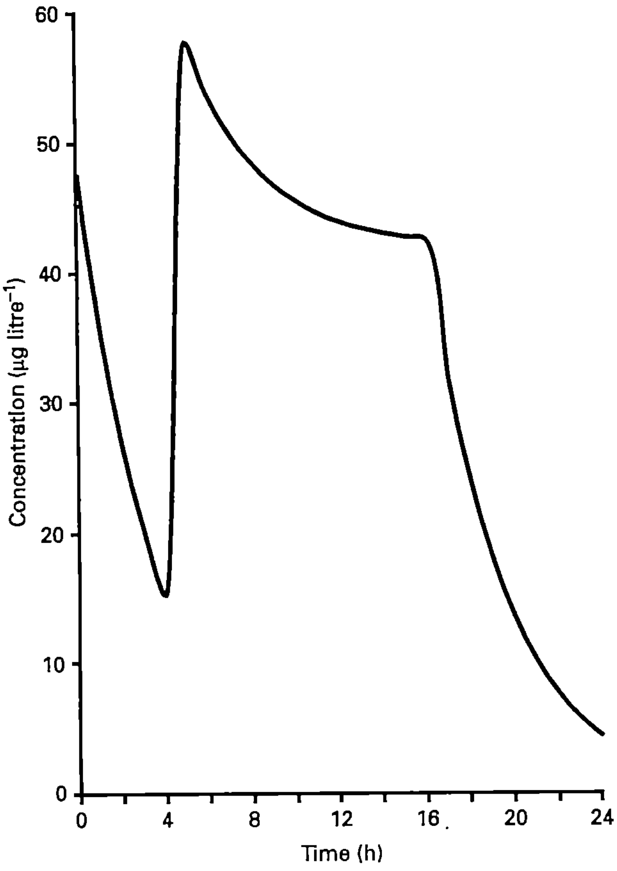

FIG. 5. A bizarre pattern that might be expected to follow first, a bolus injection of morphine 10 mg at the start, and at 4 h, a second bolus of 10 mg, given together with an infusion of 2.5 mg h^{-1} for the next 12 h.

concentration produced by the bolus—that is a value given by Xd/V where Xd is the dose. Thus the equation becomes:

$$C = \left(C^{r} + \frac{Xd}{V}\right)e^{-\frac{Cl}{V}t} + \frac{k'}{Cl}(1 - e^{-\frac{Cl}{V}t})$$

where C^{r} = residual concentration at the end of the previous section. This is a general equation which can thus be used for any bolus injection, infusion or combination. It requires us to know the clearance, the volume, the initial concentration, the sizes of any bolus and constant infusion rates. It can be simplified to:

$$C = \left(C^{r} + \frac{Xd}{V} + \frac{k'}{Cl}\right)e^{-\frac{Cl}{V}t} + \frac{k'}{Cl} \qquad (9)$$

C^{r} remains as the residual concentration present at the end of the previous phase. Figure 5 shows, with this equation, what would happen if, about 4 h after morphine 10 mg, a second bolus of 10 mg was given, with an infusion of 2.5 mg h^{-1}. The effect of the first bolus is calculated using equation (2) and, especially, the concentration at the end of 4 h. This value is substituted into equation (9) and the new pattern calculated.

The effect of the second bolus is to increase the concentration to greater than the steady state value which is approached over the next few hours. When the infusion is stopped, the usual exponential decay is seen. In general, equation (9) allows the solution of any combination of bolus and continuous infusion.

The equivalent of an "i.m." injection

So far, we have assumed that any bolus dose given is mixed instantaneously throughout the compartment, but in practice we may be giving the bolus into another site (the i.m. injection) from which it is absorbed into the main compartment. The rate at which absorption occurs is greatest when the concentration is greatest and declines with time—it is another example of exponential decay. We also assume that drug does not return from the main compartment to the injection site. This is realistic, given the size of the injection site—a few millilitre at the most. The concentration of drug at the injection site at a given time (C_1) is given by:

$$C_1 = C_1^{0}.e^{-kt}$$

where k = the rate constant for absorption. The loss from the injection site is the same as the rate of uptake into the main compartment and we can write:

$$\Delta Xd_{in} = \Delta t.C_1.k$$

or:

$$\Delta Xd_{in} = \Delta t.C_1^{0}e^{-kt}.k$$

As always, the rate of loss from the compartment is proportional to the concentration and the loss in any small interval is given by:

$$\Delta X^{0} = -\Delta t.C.Cl$$

The net change is the difference:

$$\Delta X = \Delta t(C_1^{0}.e^{-kt}.k) - C.Cl$$

To obtain concentrations, we need to divide both sides by the volume (V) and the differential equation for the instantaneous rate of change of concentration becomes:

$$\frac{dC}{dt} = \frac{C_1^{0}.k}{V}e^{-kt} - C\frac{Cl}{V}$$

As before, this can be rearranged to:

$$\frac{dC}{dt} + C\frac{Cl}{V} = \frac{C_1^{0}k}{V}k$$

The Laplace transforms for the terms on the left of the equation have been used before. The transform for that on the right is the one the inverse transform of which we have used to develop the formula for exponential decay. Thus the transformed equation is:

$$s.g(s) - C^{0} + \frac{Cl}{V}g(s) = \frac{C_1^{0}k}{V}\frac{1}{s+k}$$

If we assume that there is initially no drug present (that is, C^{0} is nil) the equation can be rearranged to:

$$g(s) = \frac{C_1^{0}k}{V}\frac{1}{s+k}\frac{1}{s+\frac{Cl}{V}}$$

The inverse transform for the last two components of the right hand side is more complex than usual—the terms are equivalent to the expression

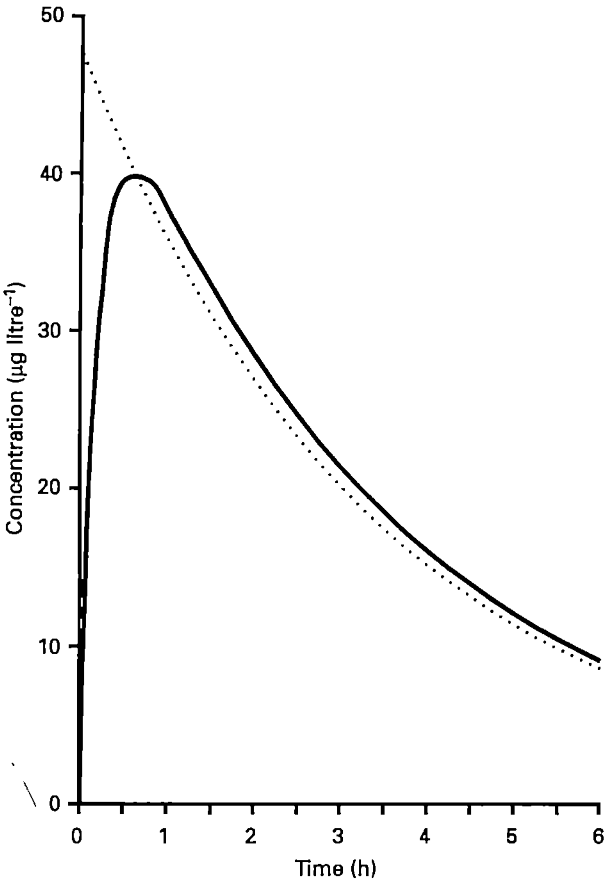

FIG. 6. Comparison of the concentration curves after either an i.v. bolus (····) of morphine 10 mg or an i.m. injection (——) of the same dose where the rate constant for absorption from the i.m. site is 5 h^{-1} (or 0.833 min^{-1}). The concentration initially is greatest after the i.v. bolus, but after about 45 min that after the i.m. injection is greater.

$1/((s+a)(s+b))$, where a and b are two constants which are neither zero nor equal to each other. The inverse transform is then (Appendix 1):

$$\frac{1}{a-b}(\mathrm{e}^{-bt}-\mathrm{e}^{-at})$$

and thus the basic equation is:

$$C=\frac{C_1^{\,0}}{V}\frac{k}{k-\frac{Cl}{V}}(\mathrm{e}^{-\frac{Cl}{V}t}-\mathrm{e}^{-kt}) \tag{10}$$

Should we be considering a process in which not all the drug is absorbed, or some is degraded before it reaches the main compartment, then we can multiply this equation by a factor, F, which expresses the bioavailability.

Figure 6 compares the effect of a bolus injection of morphine into the main compartment with that of one administered as an i.m. injection. I have assumed that the i.m. injection leads to a peak value in about 30 min. For that to happen, the rate constant (k) for the absorption has been given a value of 5 h^{-1}. It is obvious that the peak value is smaller than with the i.v. injection, but after about 45 min the concentration after the i.m. injection is slightly greater than that after the instantaneous bolus. What is happening is that the absolute amount of drug removed is greatest when the concentration is greatest, and that occurs early with the i.v. bolus. If the two curves were to be extended to an infinite time, the two areas under the curves would be the same. If the bioavailability after the i.m. injection was less, the area under that curve would be smaller than that under the instantaneous bolus curve.

Sequential "i.m." injections. If we are looking at sequential injections, we have to keep the term C^0 for the initial concentration. The Laplace transform then becomes:

$$g(s)=C_1^{\,0}\frac{k}{V}\left(\frac{1}{s+k}\right)\left(\frac{1}{s+\frac{Cl}{V}}\right)+\left(\frac{C^0}{s+\frac{Cl}{V}}\right)$$

The first term on the right transforms back as before and the second is an example we have seen, which gives the exponential decay; thus:

$$C^0=C_1^{\,0}\frac{k}{V}\left(\frac{k}{k-\frac{Cl}{V}}\right)(\mathrm{e}^{-\frac{Cl}{V}t}-\mathrm{e}^{-kt})+C^0\mathrm{e}^{-\frac{Cl}{V}t} \tag{11}$$

In general, this equation makes sense. At the time of the initial injection the concentration must be nil (e^{-0} is 1) so the first term disappears. If there is already drug in the compartment, then that is the

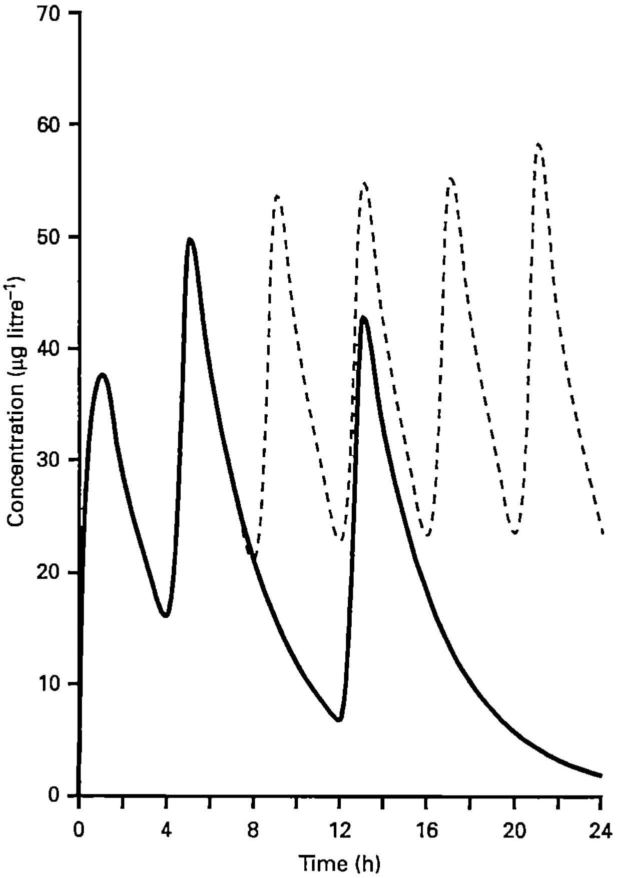

FIG. 7. Effects of multiple i.m. injections of morphine 10 mg. After an initial bolus of 10 mg and a second one after 4 h, the dashed curve shows what might be expected with repeated injections at 4-h intervals: the concentration oscillates between 30 and 50 µg litre^{-1}. With an "as required" pattern, the third injection is given at 12 h and the concentrations achieved are much smaller.

initial value. At an infinite time after the injection, the concentration must also be nil. As with equation (8), this can be used to calculate sequentially the concentrations at any time after a series of injections—provided we know the size of each injection and the time intervals.

Figure 7 illustrates what might be expected after the not uncommon pattern of using i.m. injections on a "as needed" basis. Suppose the first injection is given in the postoperative recovery room and a second about 4 h later. The third is given after another 8 h. The pattern is of large fluctuations in blood concentration and the likelihood of having a less than effective concentration for much of the time. A more effective schedule is also shown, with which the drug is given at 4-h intervals. The concentration oscillates throughout the therapeutic range.

CAUTION

The equations developed here are for the simplest kinetic model—the one-compartment system. Such a simplification may be dangerous if carried too far. In practice, it is often safer to assume at least two compartments, with a central one into which drug is given leaking out into a wider space. Hull [3] has given the necessary equations for examining what happens to boluses and i.v. infusions given into such models. Figure 8 compares the plasma morphine concentrations expected from the one-compartment model dealt with here and the three-compartment model based on data given by Aitkenhead and his colleagues [1]. The initial plasma concentrations are very much greater with the three-compartment model. Nevertheless, given that it takes some time for morphine to diffuse across the blood–brain barrier, the one-compartment model does give not too unrealistic a picture.

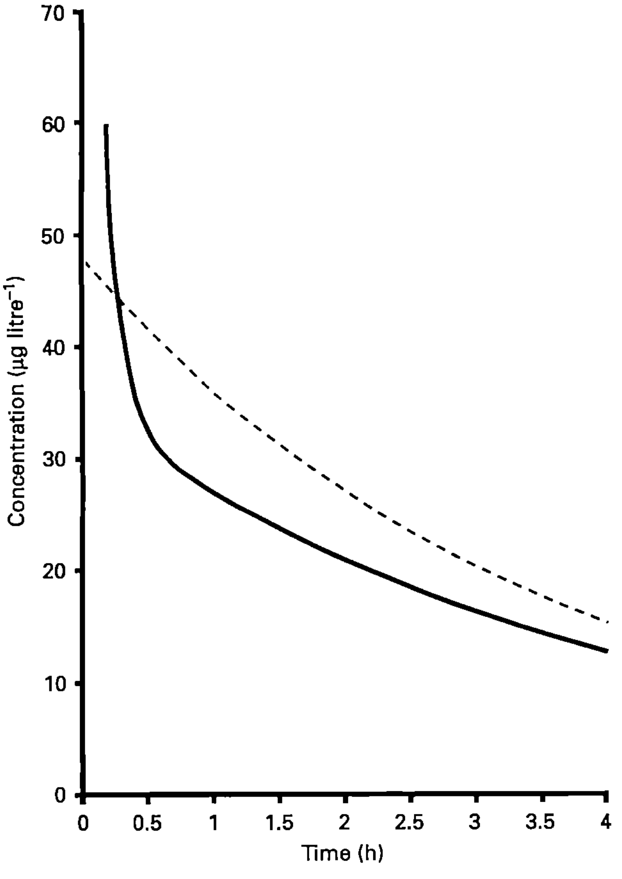

FIG. 8. Comparison of the morphine concentrations predicted with the one-compartment model (– – –) and in the central compartment of the three-compartment model (——), applying data given by Aitkenhead and colleagues [1], using the methods of Hull [3]. There is a much greater initial peak in central compartment concentration, but the decrease is, as expected, much quicker and the concentration in the compartment after about 15 min is smaller than with the one-compartment model. (Data for the three-compartment model include a volume of distribution of 227 litre and a clearance of 64 litre h^{-1}.)

The second caveat is that, although the illustrations use doses of morphine in common use in adult patients, it is vital to remember that patients differ widely, not only in their pharmacokinetics (the way they distribute and eliminate morphine) but also in their sensitivities to the effects of the drug. Each patient must be treated with due consideration of these factors.

Nevertheless, the insight gained by looking in the simplest way at what can happen with differing patterns of administration of the drug does help explain some of the variability of effect. It should also help ensure that the anaesthetist does design his dosing schedule to give the effects needed with minimal toxicity and the likelihood of a rapid recovery. To understand the model, we need to understand the mathematics behind it.

SUMMARY

The mathematical development of the equations needed to determine the plasma concentrations of drug in a one-compartment pharmacokinetic model are developed from first principles and are illustrated (with caution) by the use of morphine given by bolus or continuous i.v. injection or by a simulated i.m. injection. The equations allow the calculation of concentrations, given a knowledge of what drug is currently present, what are the sizes of the boluses by either i.m. or i.v. injection and what is the constant infusion rate. What happens when changes occur is also illustrated. The development illustrates the principles needed to apply to more complex models.

APPENDIX

THE LAPLACE TRANSFORM

The problem in looking at a biological process in which a "rate of change" occurs is that we can often write an equation showing

TABLE I. *The transforms and inverse transforms used in the paper.* a, b *and* k *are all constants.* C^0 *is the value of the function at the start—in our terms, the concentration at the start of the process*

Function $F(t)$ and inverse	Laplace transform $g(s)$
$F(1)$	$1/s$
$F(k)$ where k is a constant	k/s
e^{-at} where a is constant	$1/(s-a)$
$F(t)$	$g(s)$
$dF(t)/dt$	$s.g(s)-C^0$
$(1/a)(1-e^{-at})$	$1/(s(s+a))$
$(1/(a-b))(e^{-bt}-e^{-at})$	$1/((s+a)(s+b)$

what the rate of change is. Further, we may know the starting and finishing values. Thus we have a differential equation (one involving rates of change) and some constants at the start or end, or both. Such equations can be solved by means of the transform introduced by the mathematician P. S. de Laplace around 1780. Its virtue is that it changes the function from one involving differentials into one that can be solved algebraically. When a solution is derived it can be transformed back (the inverse transformation) into the equation we need. A good guide to the theory behind the transformation has been given by Weltner and colleagues [5] and there are also several applications in Simon's book [4]. The following account is necessarily brief.

Let the function to be transformed be $F(t)$. The transformed equation is:

$$L[F(t)] = \int_0^\infty e^{-s.t} F(t) . dt = g(s)$$

where the terms on the left and right are symbols for the transformation. What is being done is that the function is multiplied by the term e^{-st} and then integrated from zero to infinity. s, the operator, is a number which must be positive if the integral is to converge to a definite value.

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SHORT COMMUNICATIONS

A NEW TECHNIQUE FOR TWO-HAND BAG VALVE MASK VENTILATION

A. N. THOMAS, P. T. DANG, J. HYATT AND T. N. TRINH

SUMMARY

A method of bag valve mask ventilation (BVM) in which the resuscitator compresses the self-inflating bag between the open palm and body was compared with both standard single resuscitator and two-resuscitator BVM ventilation. Eighteen subjects ventilated a modified recording mannikin using each method in random order. The tidal volume (V_T*) was greater with the open palm (mean 684 (SD 182) ml) than standard single resuscitator ventilation (mean 520 (152) ml). The difference was greater in the nine subjects with small hands (mean 196 (103) ml).* V_T *was less than with two-resuscitator ventilation (mean* V_T *953 (236) ml).*

KEY WORDS
Ventilation: bag valve mask.

Ventilation with bag valve mask (BVM) systems is often inadequate when performed by a single resuscitator. One reason for this is that it is difficult to squeeze a self-inflating bag with one hand. We have postulated that this problem could be overcome by compressing the self-inflating bag between the resuscitator's open palm and his/her rib cage or iliac bone (an open-palm manoeuvre).

METHOD AND RESULTS

We studied 18 subjects who had received previous training in basic life support. Fourteen of the subjects were students, one was a nurse, and three were technical staff. In order to estimate hand size, the distance between the tip of the thumb and the fifth finger was measured on the dominant hand with the hand outstretched and the thumb fully abducted. The subject's height, age and sex were recorded also. The subject was asked to ventilate a Laerdal resusci-Annie recording mannikin in accordance with American Heart Association (AHA) guidelines [1] (12 b.p.m. of greater than 800 ml) using a BVM system (Vital Signs Code Blue BVM System). This was done for three 2-min periods; during one of these periods the open-palm manoeuvre was used and in the other periods either a standard single resuscitator or a two-resuscitator technique was used. The two-resuscitator technique was made possible by having one of the investigators hold the face mask with both hands while the subject used both hands to squeeze the self-inflating bag.

The order in which the techniques were used was randomized by the use of a sealed envelope system. Three sets of the six possible combinations in which the techniques could be used were contained in 18 sealed envelopes, one of which was given to each subject at random. Subjects were allowed to practise each technique for a few minutes before the start of the study, and at least 5 min elapsed between each set of measurements.

The number of breaths delivered to the mannikin was measured at the expiratory port of the mannikin using an Abbirico spiroflow electronic flow meter. The output signal was calibrated using a Hamilton 1-litre gas syringe (Hamilton Incorporated, Whittier, CA), and was recorded using a commercial software package [2] on a personal computer. The total expired volume was measured using a Dräger Series 2000 Minute Volume Meter, which was also placed on the expiratory port of the mannikin. Mean tidal volume (V_T) was obtained by dividing the expired volume by the total number of breaths. A repeated measures analysis of variance was used to determine if V_T differed significantly between the three methods of ventilation. The Scheffé test was then used to determine which of the techniques differed significantly from each other. The tests were repeated for all subjects and for the two sub-sets of large and small hands. The Pearson correlation coefficient (r) was used to determine if V_T and hand size were associated with each other for each of the three techniques. Significance was set at the level of 5%.

Twelve of the subjects studied were male and six female; mean age was 25.7 (SD 5.3) yr; mean weight 67.1 (15.7) kg and mean height 171 (11.3) cm. All of the subjects who started the study completed it in full. The mean hand span of all 18 subjects was 20.8 (1.7) cm, in the nine subjects with the smaller hand size, the mean span was 19.6 (1.4) cm and in the nine subjects with the larger hand size it was 22.0 (1.0) cm. Mean V_T (with SD) for each technique, together with the correlation coefficient for the relationship between hand span and V_T, and ventilatory frequency are shown in table I.

This article is accompanied by Editorial II.

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TABLE I. *Tidal volume* (V_T) *for all resuscitators and according to hand size for each method of ventilation. Ventilatory frequency* (f) *and correlation coefficients* (r) *for the relationship between hand size and* V_T *for each method of ventilation are also shown.* (*Mean values* (SD))

	Single resuscitator (standard)	Single resuscitator (open palm)	Two-resuscitator
V_T (ml)			
All resuscitators	520 (152)	684 (182)	953 (236)
Small hands	445 (136)	641 (167)	866 (166)
Large hands	595 (133)	726 (196)	1041 (271)
f (b.p.m.)	12 (3)	12 (3)	12 (1)
r	0.64	0.17	0.42

V_T was significantly greater using the open palm technique than the standard single resuscitator technique. The two-resuscitator technique, however, was superior to both single resuscitator methods and was the only technique with which the average V_T exceeded AHA guidelines. The relationship between hand size and V_T was significant only for the standard single resuscitator technique—a result which is in accordance with previously published work [3]. The difference between the single resuscitator techniques was significant in the nine subjects with the smallest hand size (mean difference 164 ml), but did not reach significance in the nine subjects with larger hands (mean difference 131 ml).

COMMENT

Our study emphasizes the well recognized inability of most resuscitators to deliver an adequate tidal volume using the standard technique of compressing a self-inflating bag. We have also confirmed the very considerable improvement that can be made by using a two-resuscitator technique [4, 5]. Unfortunately, two resuscitators are not always available to provide ventilation during life support and it is in this situation that the open-palm method of ventilation is a useful alternative, particularly when used by resuscitators with small hands. Although variations of open-palm ventilation are probably used quite widely, we could find only one previous description of any method of ventilation similar to that we have described [6]. This method can be modified by allowing the resuscitator to place one flexed knee next to the patient's head and compressing the self-inflating bag between the open palm and the anterior aspect of the thigh; this may be useful if the patient is on the floor or on a bed but with the head not at the end of the bed.

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TOPICAL ANAESTHESIA FOR EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

P. F. McDONALD AND A. M. BERRY

SUMMARY

We have investigated 60 patients in a prospective double-blind, placebo-controlled study to assess the efficacy of EMLA (Eutectic Mixture of Local Anaesthetics) cream to provide analgesia during extracorporeal shock wave lithotripsy (ESWL) with a second generation lithotriptor. Before operation, EMLA or placebo cream was applied to the patient's back at the anticipated shock head–skin interface. During the procedure increments of fentanyl 0.5 μg kg^{-1} were given i.v. on patient demand. There was no significant difference (P = 0.83) in the dose of fentanyl given to each group. We cannot recommend, therefore, the use of EMLA cream as an analgesic during ESWL with a second generation lithotriptor.

KEY WORDS

Anaesthesia: topical. Surgery: extracorporeal shock wave lithotripsy.

Over the past decade, extracorporeal shock wave lithotripsy (ESWL) has been developed and used extensively in the management of urinary tract stones. With the first generation lithotriptors, it was necessary for patients to have general, extradural or spinal anaesthesia [1]. The changed physical parameters of shock wave generator energy and focusing devices of the more recent second generation machines, such as the Storz Modulith SL 20, have reduced the need for general or regional anaesthesia. Patients may be managed now using neuroleptic techniques or i.v. analgesia alone [1]. As these patients are usually managed as outpatients, it would be advantageous to keep the level of sedation to a minimum without compromising patient comfort.

The aim of this study was to investigate if the application of the topical anaesthetic cream, Eutectic Mixture of Local Anaesthetics (EMLA), to the skin area exposed to the shock wave, reduced the analgesic requirement for fentanyl during ESWL.

METHOD AND RESULTS

The study was approved by the Hospital Ethics and Drugs committee. Informed written consent was obtained from each patient who agreed to take part in the study.

We studied 60 patients of physical status ASA I or II, with uncomplicated renal calculi and undergoing ESWL for the first time.

Astra Pharmaceuticals provided 60 identical, 60-g tubes, numbered from 1 to 60. Fifty percent of the tubes contained EMLA cream and the other 50% contained a placebo cream. The order of tubes had been distributed randomly by the company.

The patients were admitted as outpatients and numbered consecutively from 1 to 60. A 400-cm^2 area was demarcated on the patient's back at the anticipated site of the shock head coupling. One hundred minutes before the expected start of the procedure, 60 g of cream was applied to the area and covered by an occlusive dressing. The cream and occlusive dressing were left in place throughout the procedure. No other premedication was given.

The patients were positioned supine on the lithotripsy machine and the stone localized by fluoroscopy and ultrasound. The shock head was positioned such that the shock head–skin interface was over the demarcated area. Care was taken to ensure that air was not trapped at the interface. An i.v. infusion of compound sodium lactate solution 1 litre was commenced and metoclopramide 10 mg given i.v. Each patient was monitored with pulse oximetry, ECG and non-invasive arterial pressure.

ESWL was commenced at a generator voltage of 12 kV. The generator voltage was increased to 18 kV or 19 kV over the first 250 shocks and maintained at these values for the remainder of the procedure. The patients were advised to request analgesia if they experienced discomfort or pain. If they requested analgesia, they were given fentanyl 0.5 μg kg^{-1} i.v. and this dose was repeated as required throughout the procedure. Supplementary oxygen was given if necessary.

The EMLA cream was regarded as being effective if the dose of fentanyl was reduced by 50%. Statistical significance ($P < 0.05$) was tested using Student's t test.

The two groups were comparable in age, sex distribution, weight and height. Two patients were excluded from the placebo group because at operation it was found that their stones had passed into the ureter. There was no significant difference

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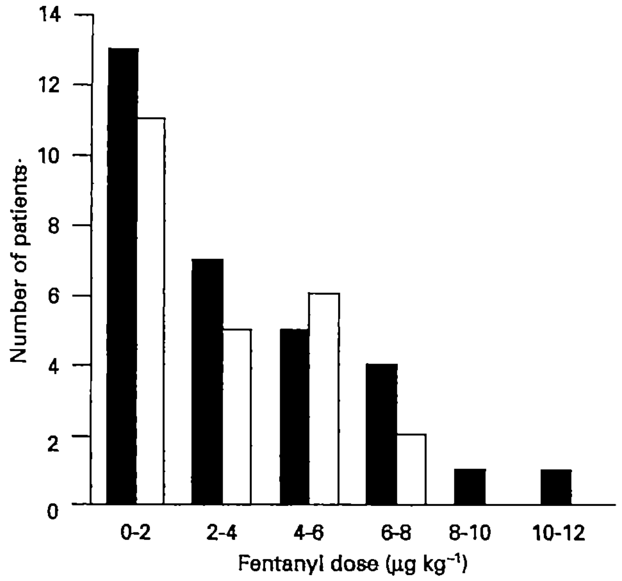

FIG. 1. Dose of fentanyl required to provide analgesia during ESWL in patients receiving either EMLA (■) or placebo cream (□).

between the two groups in respect of the time the cream had been applied before the procedure, the operation time, the stone size treated, the number of shocks administered and the maximum generator voltage used.

The mean dose of fentanyl given to the EMLA group was 3.5 (SD 2.9) µg kg^{-1}, compared with 3.1 (1.8) µg kg^{-1} for the placebo group (fig. 1) (ns: P = 0.49). As the distribution was skewed in both groups, a log transformation was made to the data. The geometric mean value for the EMLA group was 1.82 (1.39) µg kg^{-1} compared with 1.89 (1.08) µg kg^{-1} for the placebo group (ns).

COMMENT

During ESWL, a shock wave is generated from within a water cushion. The shock wave is then focused by reflectors, onto the renal calculi. In order to reach the stone, the shock wave has to pass through the water cushion, the water cushion–skin interface and the body tissues. When the shock wave passes through substances of different acoustic impedances, some energy is reflected and dissipated. The greater the difference in acoustic impedance, the greater the dissipation of energy. Other than when the shock wave passes through the stone, the greatest difference in acoustic impedance probably occurs at the water cushion–skin interface [1].

The sensation experienced by patients undergoing ESWL is described initially as a sharp stinging pain at the skin, which intensifies to a "thumping" sensation as the energy increases. On examining the patients after operation, there is almost invariably an area of erythema, sometimes petechiae and occasionally bleeding over the area of skin through which the shock wave passes. We speculated, therefore, that a large element of the pain experienced during ESWL was from the skin surface. This is supported by other workers who have successfully used local infiltration of the skin to reduce the amount of systemic analgesia needed during ESWL [2].

The topical anaesthetic, EMLA cream, has been used successfully for painless venepuncture, removal of condylomata acuminata and harvesting of split skin grafts. It has been shown that, after an application time of 90 min, skin analgesia to a depth of greater than 4 mm can be achieved [3, 4]. Using ultrasound, Fornage and Deshayes determined the mean dermal thickness over the back to be 3.6 (0.5) mm [5]. Hence, if a large element of the pain experienced during ESWL is at the skin surface, we postulated that EMLA cream should reduce the amount of systemic analgesia required during the procedure.

Our study has shown that, when compared with placebo, EMLA cream did not reduce the amount of systemic analgesia required during ESWL with the Storz Modulith SL 20. This is in contrast with a similar study by Bierkens and colleagues [6], who showed that EMLA cream reduced fentanyl requirements during ESWL, but not significantly. However, they used a Siemens Lithostar, and even in their placebo group only 53 % of patients required fentanyl, in a mean dose of 0.98 µg kg^{-1}. In comparison, 96 % of our placebo group required fentanyl in a mean dose of 3.1 µg kg^{-1}. This highlights the variable anaesthetic requirements for ESWL with the different second generation machines.

We conclude that the pain experienced during ESWL with the Storz Modulith SL 20 is at a level deeper than the skin surface. The pain may be caused by stone movement, impingement of the shock wave on the peritoneum or renal pelvic tissues or, in occasional patients, from the shock wave accidentally hitting the 12th rib. Thus we cannot recommend topical anaesthesia for lithotripsy with the Storz Modulith SL 20.

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TRANSIENT BRADYCARDIA ASSOCIATED WITH EXTRADURAL BLOOD PATCH AFTER INADVERTENT DURAL PUNCTURE IN PARTURIENTS

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SUMMARY

We have studied prospectively 10 ASA I or II postpartum patients after inadvertent dural puncture during labour. An extradural blood patch (autologous blood 15 ml) was performed within 18 h of delivery, with continuous EEG, upper facial EMG (Datex: Anesthesia and Brain Activity Monitor), pulse oximetry and heart rate measurement before, during and for 30 min after extradural injection. Non-invasive arterial pressure measurements (Dinamap) were recorded at 5-min intervals. After extradural blood patch, a statistically significant (Student's t test, $P < 0.05$) decrease in heart rate, from a mean baseline of 88.6 (SD 7.31) beat min^{-1} to 51.3 (7.6) beat min^{-1}, occurred within 122.6 (16.9) s from the time of the EBP. Bradycardia was observed for a mean duration of 12.4 (1.1) s. Upper facial EMG, EEG, Sp_{O_2} and arterial pressure did not change.

KEY WORDS

Anaesthetic techniques: extradural. Complications: headache.

Extradural blood patch is one of several treatments recommended for headache after dural puncture. However, neurological sequelae, including seizures [1], have been documented after the technique. Recent work suggests that an increase in intracranial pressure (ICP) occurs after extradural blood patch [2]. The purpose of this study was to document the physiological changes that happen at the time of and immediately after extradural blood patch.

METHODS AND RESULTS

After obtaining Institutional Review Board approval and patient informed consent, we examined the physiological effects of extradural blood patch in 10 ASA I or II postpartum patients requesting this treatment for postdural puncture headache.

Each patient had an extradural blood patch performed while in the sitting position. Using an aseptic technique, we administered autologous blood 15 ml at a rate of 0.5 ml s^{-1}, pausing for 10 s after each 5-ml increment to assess patient discomfort. The left lateral position was adopted immediately after removal of the Tuohy needle.

EEG (zero-crossing frequency and rms-integrated Amplitude; ZXF and MIA_{EEG}, respectively), upper facial EMG (Datex Anesthesia and Brain Activity Monitor (ABM), Datex Instrumentarium Oy, Helsinki, Finland), ECG (limb lead II), pulse oximetry and heart rate (Datex Oscar pulse oximeter) were monitored continuously, before, during and for 30 min after extradural blood patch. Heart rate changes were obtained from the pulse oximeter with the manufacturer's finger probe on the index finger. Heart rate fluctuations caused by movement artefact were detected by plethysmographic interference and rejected. Arterial pressure was measured non-invasively every 5 min during that time (Dinamap, Critikon, CA, U.S.A.).

EEG/EMG monitoring was undertaken with a Datex ABM that analysed biopotentials obtained from adhesive paediatric ECG electrodes (Red Dot infant monitoring electrode, 3M, St Paul, MN, U.S.A.) placed on the mid-forehead and mastoid process. The signal was filtered selectively to obtain spontaneous frontalis EMG (65–300 Hz) and EEG (1.5–25 Hz). Additional filtering removed the d.c. component of the a.c. signal, which prevented inaccurancies in zero-crossing frequency determination related to fluctuations in electrode impedance. Scaling of the EMG/EEG traces was non-linear and the display algorithm further modified the output of the log amplifiers to accentuate low output changes. The digital output from the ABM RS232 interface was converted to give a linear scale for analysis (see Appendix). The maximum changes in the five variables, arterial pressure, heart rate, ZXF, MIA_{EEG} and EMG were analysed.

Statistics

The data were analysed using Student's *t* test, with each patient acting as her own control. Bonferroni correction was made for the multiple within-group comparisons (P*5). Significance at the 5%

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TABLE I. *Physiological changes associated with extradural blood patch (EBP) (mean (SD)). ZXF = Zero-crossing frequency; FEMG = upper facial spontaneous electromyography; MIA_{EEG} = rms-integrated amplitude; AP = mean arterial pressure*

	Before EBP	After EBP
Heart rate (beat min^{-1})	88.6 (7.3)	51.3 (7.6)
Sp_{O_2} (%)	96 (2)	97 (2.2)
FEMG (μV)	5.1 (1.5)	4.6 (1.5)
ZXF (Hz)	5.3 (1.1)	5.6 (1.6)
MIA_{EEG} (μV)	60.7 (13.4)	48.9 (11.9)
AP (mm Hg)	76.5 (6.6)	68.9 (6.8)

level was taken to reject the Null hypothesis. Results are expressed as mean (SD) unless otherwise specified.

The average weight of the patients was 67.5 (8) kg and mean age was 22 (4) yr. Each postpartum woman exhibited a statistically significant (Student's t test, $P < 0.05$, with each patient serving as her own control) decrease in heart rate from a mean baseline of 88.6 (7.3) beat min^{-1} to 51.3 (7.6) beat min^{-1} within 122.6 (16.9) s from the time of the extradural blood patch and this reduction in heart rate was recorded for 12.4 (1.1) s. There was no significant change in arterial pressure, Sp_{O_2}, upper facial EMG or EEG (ZXF and MIA_{EEG}) (table I).

COMMENT

At full term there is an increase in blood volume within the extradural veins, a reduction in cerebrospinal fluid (CSF) surrounding the spinal cord and an increase in CSF pressure during the second stage of labour. Therefore the compliance of the extradural space is reduced. Injection of blood into the extradural space may cause an increase in ICP lasting 1–2 min [2], suggesting a Cushing response as the aetiology of the reduction in heart rate. There was no significant change in arterial pressure in this study, but a transient increase would have been missed with the frequency at which arterial pressure was measured. More frequent measurement was avoided, as patient discomfort caused by cuff inflation may have confounded the study.

Postdural puncture headache is described as resulting from continued CSF leakage. In this study, extradural blood patch was performed within 18 h of delivery.

Whole blood is a non-Newtonian fluid with a viscosity several times that of water which depends principally upon the PCV (reduced postpartum), and to a lesser extent plasma proteins (increased postpartum), blood flow velocity (an inverse relationship exists) and the Fahraeud–Linquist effect (rouleaux formation). Clot formation also impedes the removal of blood from the extradural space. This may further compound the problems discussed above.

A temporal relationship between ICP and facial EMG fluctuations has been reported, the latter increasing consistently 30 s after an increase in ICP [3]. However, an increase in facial EMG was not detected in this study. Measurement of EEG (ZXF and MIA_{EEG}) with the Datex ABM in awake patients is likely to have considerable contamination from low frequency scalp EMG and this may have masked any changes in true EEG. There was a reduction in MIA_{EEG}.

An alternative explanation for the bradycardia associated with extradural blood patch is formation of free radicals ($R^{\cdot}$). Free radical formation in this situation may have been the result of a reaction between ferrous ions and hydrogen peroxide, the Fenton reaction (equation (1) below) or the iron-catalysed Haber–Weiss type reaction (equation (2) below) [4]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^{-} \qquad (1)$$

$$O_2^{\cdot} + H_2O_2 \xrightarrow{\text{[Fe salt: catalyst]}} O_2 + OH^{\cdot} + OH^{-} \qquad (2)$$

Free radicals can also be formed by mechanical forces, including homolytic breaking of main chain bonds in polymers and charge transfer (the triboelectric effect) [5]. Because of their reactivity, most free radicals exist only at small concentrations (10^{-4}–10^{-9} mol $litre^{-1}$) and do not travel from the site of formation. However, although the initial free radical produces only local effects, the secondary radicals formed by chain reactions initiated by the free radical, and the degradation products produced by reactions involving free radicals, can have biological effects distant from the site where the first free radicals were produced [4].

Free radicals may alter transmembrane movement of ions through membrane channels, including ion exchange mechanisms in the cardiac sarcolemma. Primary and secondary free radical injury may have a profound effect on the electrical function of the myocardium [6].

It would appear that extradural injection of 15 ml of whole blood in the immediate postpartum period caused a decrease in heart rate. As a result of our preliminary findings, we recommend ECG monitoring and care in the use of an extradural blood patch in patients with pre-existing cardiac disease or intracranial pathology.

APPENDIX

The formula below produces a curve that is very close to that of the actual output of the ABM:

$$Y = \left(\frac{X}{141}\right)^{4.6} + 0.6$$

For byte values less than 168 (3 μV) there is some loss of accuracy and the formula below was used:

$$Y = (x \times 0.0198 - 3.3) + 3$$

These formulae were entered into a spread sheet macro to convert the ABM byte output into microvolts.

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EFFECTS OF OMEPRAZOLE, RANITIDINE, FAMOTIDINE AND PLACEBO ON GASTRIC SECRETION IN PATIENTS UNDERGOING ELECTIVE SURGERY

F. ESCOLANO, J. CASTAÑO, R. LOPEZ, E. BISBE AND A. ALCON

SUMMARY

We have compared the effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in a double-blind study in 110 patients undergoing elective surgery. Three hours before operation, the patients received, orally, omeprazole 40 mg, ranitidine 150 mg, famotidine 40 mg or placebo. Gastric volume and pH were measured immediately after induction of anaesthesia. Omeprazole, ranitidine and famotidine produced a significant increase in gastric pH and a significant decrease in gastric volume compared with placebo. When the effects of omeprazole on gastric volume were compared with those of ranitidine and famotidine, no significant difference was found, but omeprazole was significantly less effective in increasing gastric pH. The number of patients having a pH less than 2.5 and a volume greater than 0.4 ml kg^{-1} were: none in the ranitidine group, one (3%) in the famotidine group, four (15%) in the omeprazole group and six (23%) in the placebo group. We conclude that omeprazole 40 mg given 2–4 h before surgery does not afford adequate prophylaxis for the acid aspiration syndrome.

KEY WORDS

Gastrointestinal tract: gastric secretion. Pharmacology: famotidine, omeprazole, ranitidine. Premedication.

Several studies have shown that the gastric fluid pH is an important factor causing pulmonary damage after aspiration of gastric contents. A pH less than 2.5 and a gastric volume greater than 0.4 ml kg^{-1} are suggested as being risk factors for the acid aspiration syndrome in adults [1]. Thirty to fifty percent of normal adults undergoing elective surgery have a lesser gastric pH and greater volume [1, 2] and one of the aims of preoperative treatment should be reducing these risk factors. Many drugs have been used to achieve this objective. The H_2-receptor antagonists produce an effective reduction in gastric volume [1, 2], but do not modify the pH of the gastric fluid already present in the stomach. Therefore, the protection obtained with these agents depends on the dose of drug and the time elapsed between its administration and the aspiration of fluid [2].

Omeprazole is a substituted benzimidazole, non-competitive inhibitor of gastric secretion. It blocks H^+/K^+-ATPase, the proton pump of the parietal cell. Because of its pharmacokinetic characteristics, omeprazole may offer certain advantages compared with H_2-receptor antagonists, with respect to potency and duration of action [3].

The aim of this study was to compare the effects of omeprazole, ranitidine, famotidine and placebo on gastric volume and pH in patients undergoing elective surgery under general anaesthesia.

METHODS AND RESULTS

The study was approved by the Hospital Ethics Committee and 110 patients (47 male), ASA I–III, aged 15–83 yr (mean 54 yr), undergoing elective surgery were studied after informed consent had been given. The patients were allocated randomly to one of four groups: group A ($n = 27$) received omeprazole 40 mg; group B ($n = 17$) received ranitidine 150 mg; group C ($n = 30$) received famotidine 40 mg; group D ($n = 26$) received placebo. The drugs were administered orally 3 h before induction of anaesthesia, together with 20 ml of water and oral lorazepam 1–2 mg, depending on the weight and physical condition of the patient. Patients with significant liver, kidney or gastrointestinal diseases, those who were pregnant, hypersensitive to drugs, receiving antacids or H_2-receptor antagonists or undergoing gastrointestinal surgery were excluded.

The study was carried out in a double-blind manner. Age, weight, sex, smoking and drinking habits, fasting period and time of drug administration were recorded, as was any side effect caused by the study agents.

Anaesthesia was induced with thiopentone followed by atracurium. After 3 min of manual ventilation of the lungs, the trachea was intubated. Anaesthesia was maintained with 70 % nitrous oxide in oxygen supplemented with volatile agents or opioids. Anticholinergic agents were avoided until

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TABLE I. *Volume and pH values of gastric fluid samples (mean* (SD) *[range]), and subjects deemed at risk of acid aspiration.* **Significant with respect to placebo* (P < *0.05)*

	Volume		pH		At risk	
Group	*n*	(ml)	*n*		*n*	(%)
Omeprazole	27	11.0 (12.0) [0–53]*	24	5.1 (2.5) [1.5–8.1]*	4	15
Ranitidine	27	8.8 (8.6) [0–30]*	25	7.1 (1.6) [1.3–8.0]*	0	0
Famotidine	30	8.5 (8.8) [0–30]*	25	6.5 (1.8) [1.6–7.8]*	1	3
Placebo	26	21.2 (17.6) [1–79]	26	3.1 (2.4) [1.1–7.2]	6	23

the sample of gastric fluid had been obtained. Immediately after induction, a 16-French gauge nasogastric tube was inserted into the stomach and its correct position checked by auscultation of injected air. The gastric contents were aspirated and the volume and pH measured. The pH was measured by a pH microelectrode attached to a digital pH meter (Microph, Crison).

Data were analysed statistically using analysis of variance of a linear model in which the gastric fluid volume and pH were considered as dependent variables and were analysed separately. As independent variables, we considered: treatment (qualitative; three groups: omeprazole, ranitidine and famotidine), time elapsed between drug administration and sample extraction (min), sex (qualitative), weight (kg), age (yr), smoking (qualitative: yes or no). In this model, the constant term was represented by treatment with placebo. After the analysis of the model and the evaluation of main effects, several hypotheses were tested using an F test. These hypotheses were global comparisons between all the treatments and subsequent comparisons between pairs of treatments. The effect of treatment on the number of patients deemed "at risk" (gastric volume equal to or greater than 25 ml and gastric pH less than 2.5) were compared using the chi-square test, Yates' correction being applied when necessary.

The four groups of patients were comparable in age, weight, sex and time from drug administration to sample extraction which ranged from 80 to 330 min, being 120–240 min for 78.9 % of patients. Mean (SEM) values for the groups were: omeprazole, 180 (41.8) min; ranitidine, 185 (58.0) min; famotidine, 175 (47.5) min; placebo, 178 (58.1) min. The number of patients in each group and the gastric pH and volumes are shown in table I. The decrease in gastric volume and increase in pH in the omeprazole, ranitidine and famotidine groups were significantly different from those in the placebo group ($P < 0.05$). This was caused by drug administration and not any independent variable. No significant differences were found for gastric volume values between the treated groups ($F = 0.84$; $P > 0.05$). The increase in pH values produced by ranitidine and famotidine was significantly greater than that produced by omeprazole (ranitidine *vs* omeprazole, $F = 7.25$, $P < 0.05$; famotidine *vs* omeprazole, $F = 8.84$, $P < 0.05$), but not between famotidine and ranitidine ($F = 0.02$, $P > 0.05$).

The number of patients at risk according to the criteria of Roberts and Shirley [1] are shown in table I: four (15 %) in the omeprazole group, one (3 %) in famotidine group, six (23 %) in the placebo group and none in the ranitidine group. The difference with respect to placebo was significant only for the ranitidine group: $\chi^2 = 4.92$ ($P < 0.05$).

No side effects were observed.

COMMENT

The present study has shown that a single oral dose of omeprazole, ranitidine or famotidine, given 2–4 h before anaesthetic induction, produced a significant increase in gastric pH and a decrease in gastric fluid volume, compared with placebo. There was no significant difference in gastric volume when omeprazole was compared with ranitidine and famotidine, but ranitidine and famotidine produced a significantly greater increase in gastric pH compared with omeprazole.

The number of patients deemed at risk for the acid aspiration syndrome was greater in the omeprazole group (15 %) than in the ranitidine and famotidine groups (table I). This may be a reflection of individual differences in absorption of the drug after a single oral dose. Omeprazole is inactivated rapidly at a low gastric pH and, to avoid this, the drug is administered as enteric-coated granules for absorption in the small intestine, which may be relatively delayed. Consequently, the time to peak effect is delayed also [3].

In previous studies, doses of omeprazole 40 mg [4] and 80 mg [5] given the night before surgery reduced the number of patients deemed at risk to 5 %, while two doses of 40 mg resulted in no patients being deemed at risk [6].

It is concluded that omeprazole 40 mg given 2–4 h before operation does not increase gastric pH and decrease gastric volume to an acceptable degree in 15 % of patients. A greater dose given a longer time before anaesthesia is recommended.

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SURGICAL FACE MASKS ARE EFFECTIVE IN REDUCING BACTERIAL CONTAMINATION CAUSED BY DISPERSAL FROM THE UPPER AIRWAY

B. J. PHILIPS, S. FERGUSSON, P. ARMSTRONG, F. M. ANDERSON AND J. A. W. WILDSMITH

SUMMARY

We have studied the effectiveness of surgical face masks in reducing bacterial contamination of a surface, produced by dispersal of organisms from the upper airway. Twenty-five volunteers were asked to speak at blood agar plates positioned in close proximity to the mouth, initially whilst not wearing a face mask and then wearing a surgical face mask over the mouth and nose. A fresh face mask almost completely abolished bacterial contamination of agar plates 30 cm from the mouth. After 15 min there was an increase in the level of contamination which was statistically insignificant.

KEY WORDS

Anaesthetic techniques: regional. Complications: bacterial contamination. Equipment: surgical face mask.

A serious complication of subarachnoid block is bacterial meningitis, and a meticulous aseptic technique is vital, although one component of that, the wearing of a surgical face mask, has been questioned recently [1]. In this study, we examined the effect of wearing a face mask on bacterial contamination under conditions similar to those found during spinal anaesthesia.

METHOD AND RESULTS

Twenty-five anaesthetists (ages 25–45 yr) volunteered to take part in the study. Each sat on a chair in a draught-free room and a blood agar plate was positioned flat against the wall 30 cm away from the subject's mouth. The subject spoke directly at the agar plate for 5 min. A fresh, standard, soft, pleated, non-glass fibre face mask (Brevet) was then worn and the subject continued to speak for a further 15 min (three 5-min intervals). Further blood agar plates were positioned in front of the subject's mouth during the first and third 5-min periods.

The agar dishes were sealed and taken immediately to the Department of Clinical Bacteriology where they were incubated for 24 h at 37 °C in a carbon dioxide-rich environment. The bacterial colonies that grew were counted and identified using standard laboratory techniques. The results were analysed using ANOVA, followed by a two-sample Student's *t* test.

At least one colony grew on 13 of the 25 plates collected from unmasked subjects (mean numbers of colonies 3.6, range 0–24), whereas only three plates were found to be contaminated, with only one colony on each, when a fresh face mask was worn (fig. 1). After the face mask had been worn for 10 min, nine plates were contaminated (mean number of colonies 1, range 0–10). In this last set, only one plate grew as many as 10 colonies, the remaining eight producing between one and three colonies. The contamination of the plate was less when the subject was wearing a face mask, both fresh and worn for 10 min, than when they were unmasked. These differences were statistically significant ($P < 0.01$ fresh face mask; $P < 0.05$ worn face mask). There was no statistical difference between the numbers of colonies grown on the plates obtained at the two intervals when the masks were worn.

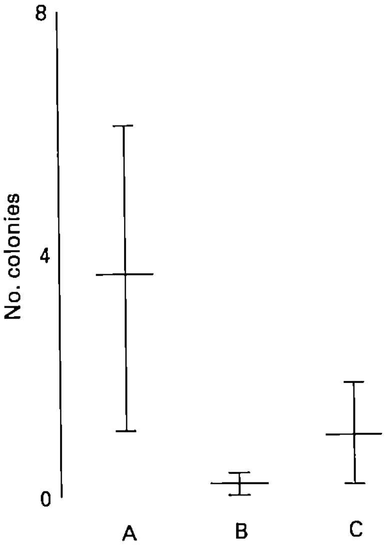

FIG. 1. Number of colonies grown in the agar plates in group A (no face mask), group B (face mask 0–5 min) and group C (face mask 10–15 min): mean number of colonies grown (horizontal bars) and 95% confidence limits (vertical bars).

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All the bacteria grown were normal upper respiratory commensals: coagulase negative Staphylococci, alpha-haemolytic Streptococci, Micrococci, *Moraxella catarrhalis* and a coliform (one colony).

COMMENT

The results indicate that wearing a face mask produced a marked reduction in the bacterial contamination of a surface in close proximity to the upper airway. Bacterial colonies grew on more than 50 % of the plates obtained while the subject was not wearing a face mask. A fresh face mask almost abolished contamination, and after 15 min wear there was only a small and insignificant increase in the number of organisms isolated.

Subarachnoid blocks are performed by a large number of anaesthetists who vary in both their technique and their experience. Similarly, the blocks vary in their degree of difficulty, from being quick and easy to being time-consuming and difficult to perform. In our study, we aimed to simulate conditions which would represent those occurring in the majority of cases in which subarachnoid blocks are sited. The agar dishes were placed at a distance and height judged to be similar to that between mouth and operating field and the area of the agar dish was similar to the opening in a sterile drape. The time intervals were chosen as being representative of how long it may take to perform a subarachnoid block.

The organisms grown were normal upper respiratory commensals. These are of low pathogenicity and virulence and are unlikely to cause infection in the wound of a patient with an intact immune system. However, the central nervous system has no such defences when its coverings are breached, and cerebrospinal fluid provides bacteria with an ideal culture medium. Bacterial meningitis is rare after subarachnoid block, but occasional reports continue to appear, usually with the source of infection unclear [2]. The diagnosis of bacterial meningitis as opposed to aseptic meningitis is often made from the CSF biochemistry rather than from positive cultures. Even so, there are reports of meningitis produced by organisms normally of low pathogenicity, such as *Streptococcus sanguis*—an alpha-haemolytic streptococcus associated usually with dental caries [3]. In that case, the probable source of infection was a blood patch performed for headache caused by accidental dural puncture, although it does illustrate that usually benign organisms may cause CSF infection. Furthermore, clinicians may carry more virulent pathogens, and we have shown that working surfaces could become contaminated with airway flora.

In a recent review, Ayliffe [4] concluded that it was probably unnecessary to wear a face mask in theatre to reduce wound infections, although he did state that there was little evidence to support this. Ritter and colleagues [5] found that the wearing of face masks made no difference to the contamination of agar dishes 1.20 m above the floor within a theatre suite. This was probably because the effect of people merely being present was so great. A similar argument could be applied to ward work, where large numbers of people are moving about and causing considerable contamination from other sources. During subarachnoid blocks, masks are likely to be far more important because the operator's airway is in such close proximity to the field of work. In our study, no attempt was made to reduce surrounding contamination, the volunteers did not wear theatre clothing and others were not excluded from the room. Nevertheless, the use of a fresh face mask virtually abolished contamination of the agar plates.

The type of mask is important. Simple paper or cloth masks provide little benefit; the most effective are large, soft, pleated and pliable masks, the actual material being unimportant [6]. The better ones, when tested *in vitro*, remained good bacterial filters for 8 h, but we found a small increase in agar plate contamination after the face mask had been worn for 15 min. Although the increase was statistically insignificant, it may be advisable to wear a fresh face mask for each procedure.

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INFLUENCE OF CARDIAC OUTPUT ON THE CORRELATION BETWEEN MIXED VENOUS AND CENTRAL VENOUS OXYGEN SATURATION

J. C. BERRIDGE

SUMMARY

The influence of cardiac output on the correlation between central venous oxygen saturation and mixed venous oxygen saturation was assessed in 51 patients who had both a pulmonary artery catheter and separate central venous catheter in situ. *Seventy-six paired samples were taken from the catheters and oxygen saturation measured immediately in a Ciba Corning 2500 Co-oximeter. Cardiac output was measured using a standard thermodilution technique. The data were separated into groups with low cardiac index* (< 2.5 *litre* $\text{min}^{-1}\,\text{m}^{-2}$; $n = 20$), *medium cardiac index* (2.5–4.0 *litre* $\text{min}^{-1}\,\text{m}^{-2}$; $n = 36$) *and high cardiac index* (> 4.0 *litre* $\text{min}^{-1}\,\text{m}^{-2}$; $n = 20$). *The correlation coefficients of the three groups were: low cardiac index 0.95, medium cardiac index 0.88 and high cardiac index 0.95* ($P < .001$ *for all three groups). All measurements were made before any x-ray and necessary repositioning of the central venous catheter. These results suggest that central venous oxygen saturation is a useful estimate of mixed venous oxygen saturation and that the influence of cardiac output on that estimate is minimal.*

KEY WORDS

Heart: cardiac output. Measurement techniques: central venous saturation, mixed venous saturation.

Mixed venous oxygen saturation ($S\bar{v}_{O_2}$) is a valuable measurement in monitoring the critically ill [1]. However, this information can be obtained only from a correctly positioned pulmonary artery catheter. Insertion of these catheters is not devoid of risk and often the constraints of emergency anaesthesia preclude successful insertion. In contrast, central venous catheterization is an extremely common and valuable technique in emergency anaesthesia. Previous studies, both in animals [2] and in the critically ill [3, 4] have shown a good correlation between central venous oxygen saturation (Scv_{O_2}) and $S\bar{v}_{O_2}$. These studies did not examine the effect of cardiac output on this correlation, were performed in only a few subjects and samples were taken from the central venous catheter only after x-ray control and correct positioning of the catheter.

The aims of this study were to investigate the effects of cardiac output on the correlation between the two oxygen saturations and determine whether or not a good estimate of $S\bar{v}_{O_2}$ could be obtained from a central venous catheter positioned clinically.

METHODS AND RESULTS

Seventy-six paired samples of blood from the distal lumen of a pulmonary artery catheter and a simultaneously placed central venous catheter were taken from 51 patients. The oxygen saturation was measured immediately in a Corning 2500 Co-oximeter. Cardiac output was measured using a standard thermodilution technique at that time and cardiac index calculated from the body surface area, which was determined using a standard nomogram from the subject's height and weight. Low cardiac index was defined as being < 2.5 litre $\text{min}^{-1}\,\text{m}^{-2}$ ($n = 20$), medium cardiac index between 2.5 and 4.0 litre $\text{min}^{-1}\,\text{m}^{-2}$ ($n = 36$) and high cardiac index > 4 litre $\text{min}^{-1}\,\text{m}^{-2}$ ($n = 20$). There were 34 male and 17 female patients (mean age 60.8 yr); 23 had ischaemic heart disease and were undergoing coronary artery bypass grafting, 10 were undergoing mitral valve replacement and eight, aortic valve replacement. There were two cases of sepsis, two of trauma and one aorto–bifemoral graft in a patient with hypertrophic cardiomyopathy.

The results are summarized in table I. Each correlation coefficient is a Pearson correlation coefficient (r) with $S\bar{v}_{O_2}$ being the dependent and Scv_{O_2} the determining variable. All values of r are highly significant ($P < 0.001$), but there was no statistically significant difference between the groups. Overall, Scv_{O_2} was 3.1 % (95 % confidence interval 2.4–3.75) greater than $S\bar{v}_{O_2}$. The samples were taken before the check x-rays which confirmed correct placement of the pulmonary artery catheters in all patients. In addition to excellent correlation, in the 25 patients who had two sampling points, the changes in Scv_{O_2} correlated well with the change in $S\bar{v}_{O_2}$.

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TABLE I. *Relationship between cardiac output (cardiac index, CI) and the correlation between mixed venous ($S\bar{v}_{O_2}$) and central venous (Scv_{O_2}) oxygen saturations (mean (95% confidence interval)).* r = *Pearson's correlation coefficient*

	Low CI	Medium CI	High CI	Total
n	20	36	20	76
CI	2.0 (1.76–2.14)	3.2 (3.04–3.32)	4.9 (4.47–5.23)	3.3 (3.01–3.59)
$S\bar{v}_{O_2}$	66.8 (62.48–71.2)	71.2 (69.01–73.39)	74.2 (71.17–77.23)	70.8 (69.06–72.62)
Scv_{O_2}	70.2 (66.85–75.55)	74.3 (72.19–76.41)	77 (74.51–79.48)	73.9 (72.25–75.63)
$(Scv_{O_2} - S\bar{v}_{O_2})$	3.5 (2.17–4.79)	3.1 (2.06–4.14)	2.8 (1.8–3.86)	3.1 (2.45–3.75)
r	0.95 (0.87–0.98)	0.88 (0.78–0.94)	0.95 (0.87–0.98)	0.93 (0.89–0.96)

COMMENT

These results suggest that Scv_{O_2} is a good estimate of $S\bar{v}_{O_2}$, even when the exact position of the central venous catheter is unknown. The effect of cardiac output on that estimate is minimal. These findings suggest that central venous sampling in emergency situations can be useful in estimating Sv_{O_2}, oxygen extraction ratio and arterio–venous oxygen content difference.

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A METHOD TO FACILITATE REGIONAL ANAESTHESIA BY DETECTION OF MIXED NERVE ACTION POTENTIALS

M. Y. K. WEE, A. GEEURICKX AND S. WIMALARATNA

SUMMARY

We have studied conduction anaesthesia of the median and ulnar nerves at the axilla using mixed nerve action potentials (MNAP) as a guide to needle position in three volunteers. The median and ulnar nerves were stimulated distally at the wrist using surface electrodes and MNAP were detected proximally in the axilla using an insulated needle electrode. The increase in amplitude of MNAP to maximum as the insulated needle electrode approached the nerve trunk was taken as an indication that the tip of the needle was in close proximity to the nerve trunk. Instillation of 1% lignocaine plain 4 ml decreased the amplitude of the MNAP with the onset of nerve block. We conclude that this method may be of potential use as an aid to peripheral regional anaesthesia by allowing accurate localization of needle position close to specific nerve trunks.

KEY WORDS

Anaesthetic techniques: regional. Measurement techniques: mixed nerve action potentials.

There are several factors which may discourage the anaesthetist from using regional anaesthesia, not least the uncertainty of success. Several methods have been described to increase the success of regional anaesthesia, including eliciting paraesthesiae, the use of a peripheral nerve stimulator [1–3] and, most recently, ultrasound [4]. However, they all have some disadvantages. The detection of mixed nerve action potentials (MNAP) has been established by neurophysiologists [5, 6], but to our knowledge has not been applied to the clinical use of regional anaesthesia. The aim of this study was to determine if the detection of MNAP may be a useful aid to regional anaesthesia.

METHODS AND RESULTS

Local Ethics Committee approval was obtained for the study. Anaesthetists in training and an ambulance paramedic were used as volunteers. Full informed consent was obtained from each volunteer and they allowed one of their upper limbs to be studied each session.

A Dantac 1500 EMG apparatus was used to provide both stimulation and detection of MNAP. The peripheral median or ulnar nerve was stimulated distally at the wrist using a bipolar surface stimulator (DISA) delivering a 0.2-ms square wave pulse at a frequency of 1 Hz. This elicited a tingling sensation of mild to moderate nature at the wrist, with a stimulation intensity of 8–15 V. MNAP were recorded proximally using a disposable, 23-gauge, 50-mm length Teflon-sheathed Pole needle. The Pole needle acted as the recording electrode (cathode), whilst the reference electrode (anode) was a silver disc smeared with electrolyte jelly attached to the skin close to the point of insertion. An earth strip (ground electrode) soaked in saline was wrapped around the arm between the stimulator and the recording electrode. The axillary artery was used as the anatomical landmark for the approach to the brachial plexus in the axilla.

After s.c. infiltration of the skin with 1% lignocaine, the Pole needle was inserted so that the uninsulated tip was positioned subcutaneously. The intensity of the stimulus delivered by the distal stimulating electrode was reduced until the smallest amplitude MNAP was recorded by the Pole needle. The Pole needle was then advanced towards the neurovascular bundle until a maximum MNAP was obtained. This was taken as the point of closest approximation to the nerve trunk. The Pole needle was fixed in position and 1% lignocaine plain 4 ml injected via the side port of the needle. The neurovascular sheath was occluded distal to the needle insertion using digital pressure for a period of approximately 5 min. Sensory block was confirmed by testing pinprick sensation and demonstrating an increase in sensory threshold to electrical stimulus.

The MNAP were recorded in stages: s.c., at the point of closest proximity to the nerve trunk and after instillation of local anaesthetic at 0, 3, 5, 10 and 15 min.

There were four successful median and ulnar nerve blocks and no failures. The decrease in amplitude of the MNAP immediately after instillation of local anaesthetic at time 0 was probably the result of a spatial conduction barrier caused by the

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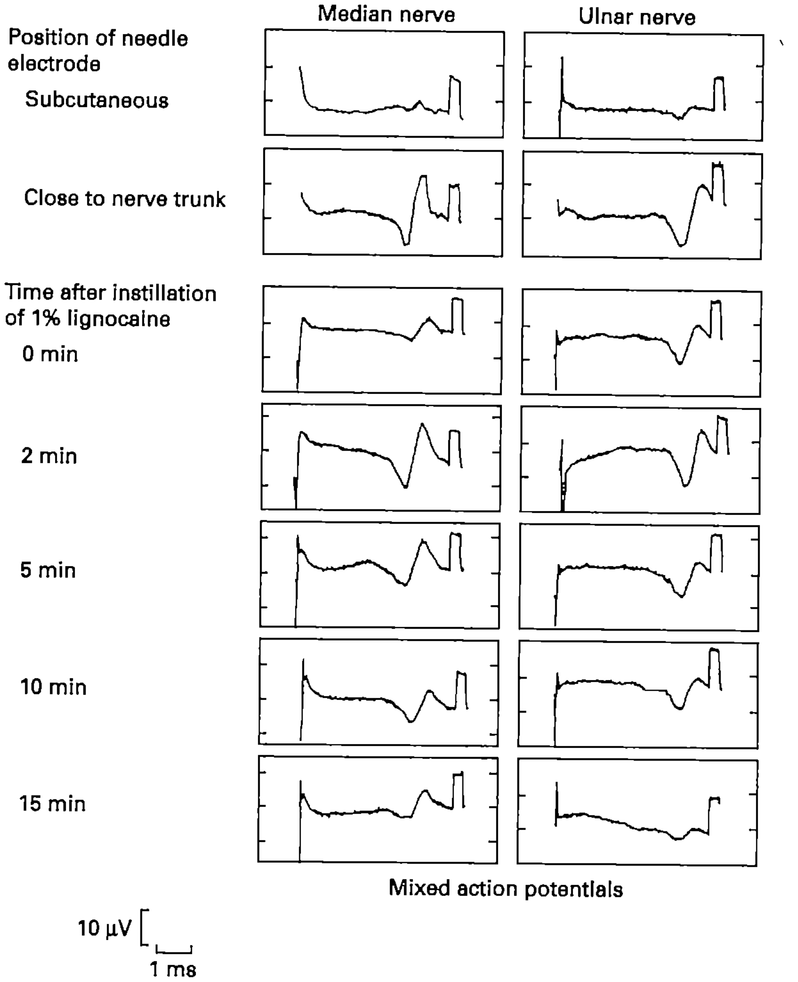

FIG. 1. Recordings of median and ulnar mixed nerve action potentials.

volume of local anaesthetic between the needle and the nerve (fig. 1). At 2 min, the amplitude of the MNAP had increased in size, possibly signifying dispersion of local anaesthetic within the sheath and approximation of the needle to the nerve as a consequence. At 5 min, the amplitude of the MNAP had reduced in size as a result of the action of local anaesthetic on the nerve. A progressive reduction in the amplitude of the MNAP was noted at 10 and 15 min, by which time clinical block was obvious to the volunteer. Sensory block was confirmed by demonstrating the increase in sensory threshold to electrical stimulus by approximately 90 %. The rapid onset of anaesthesia (mean 5.2 min, range 3–7 min), despite the small dose of local anaesthetic used, confirmed indirectly the proximity of the Pole needle to the nerve trunk. The mean (range) duration of anaesthesia was 78.6 (64–94) min for the median nerve and 82.5 (70–98) min for the ulnar nerve.

COMMENT

This study has demonstrated that MNAP generated by distal stimulation may be used as a guide to accurate needle placement on specific nerve trunks. The results were consistent and reproducible. The "pop" felt when the needle enters the neurovascular axillary sheath has often been described as a good indicator of correct needle placement. It was interesting to note that, on several occasions when a pop was felt, there were no discernible increases in MNAP. This probably indicated that the Pole needle may have been in the sheath but not necessarily close to the nerve trunk.

The accuracy of the placement of the block needle may potentially allow a reduction in the dose of local anaesthetic used without sacrificing the success of the block. We have demonstrated that an effective conduction block could be achieved by using a low dose of local anaesthetic. The reason for this was probably accurate needle placement. The sensory block obtained with 1 % lignocaine 4 ml seemed to have been complete. The advantage of this method over a peripheral nerve stimulator is that it avoids direct stimulation of muscle, which may give false positive results [2], and avoids pain experienced by some patients either when the nerve trunk is stimulated directly [3] or if direct motor nerve stimulation causes muscle contraction at the site of injury. Development of simple apparatus to allow distal nerve or dermatomal stimulation and the detection of proximal MNAP should facilitate introduction of the technique into clinical practice.

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CASE REPORTS

LUMBOVERTEBRAL SYNDROME AFTER EXTRADURAL BLOOD PATCH

M. D. SEEBERGER AND A. URWYLER

SUMMARY

We describe a patient who developed an immobilizing lumbovertebral syndrome after an extradural blood patch and who was hospitalized with a suspected extradural abscess. An infectious aetiology of the persistent backache could be excluded and the patient recovered with analgesics and physiotherapy. The probable aetiology is discussed.

KEY WORDS

Anaesthetic techniques: extradural (blood patch). Complications: lumbovertebral syndrome.

CASE REPORT

A 40-yr-old patient was scheduled for repair of torn anterior fibulotalus and fibulocalcaneal ligaments. In her past medical history it was notable that twice before she had been admitted to hospital for treatment of lumbovertebral syndromes elicited by weight-lifting. As a result of this previous condition, 5 years previously she was obliged to change her profession from a nurse to a medical clerk. Since then, she had never had a severe backache, although she regularly suffered from migraine. Otherwise, she was in good health. According to the patient's wishes extradural anaesthesia was planned.

After oral preanaesthetic medication with midazolam 15 mg, the patient was alert but calm upon arrival in the operating room. With the patient in the lateral position, the first attempt at placing an 18-gauge Tuohy extradural needle resulted in accidental penetration of the dura at the L3–4 level. Therefore, single-shot spinal anaesthesia was performed with plain 0.5% bupivacaine 17.5 mg via the Tuohy needle. The further intraoperative course was uneventful.

On the morning of the first day after operation, the patient complained of nausea. On the same afternoon, severe frontal and occipital headache occurred which were made worse by sitting and improved on lying down. A low cerebrospinal fluid (CSF) pressure headache was diagnosed. Using conservative treatment with initial bed rest, oral analgesics and adequate hydration, which included increased coffee drinking, the postdural puncture headache (PDPH) improved markedly. The patient, who had a unilateral plaster of Paris dressing, began walking with crutches and was allowed home 8 days after operation, with minimal headache.

With the greater activity and cessation of bed rest, the PDPH worsened. After initially refusing, the patient finally decided to accept an extradural blood patch (EBP) on day 12 after operation. After monitoring the patient with a sphygmomanometer, ECG and pulse oximeter, she was placed in the left lateral decubitus position. Using strict aseptic techniques, the interspace of the previous dural puncture was identified and an 18-gauge Tuohy needle was inserted into the extradural space. Thirty millilitre of blood was aspirated aseptically through a 16-gauge i.v. catheter placed in a large vein at the antecubital fossa. This blood was injected slowly into the extradural space, with pauses after 15 and 20 ml. After 25 ml had been injected, the patient reported the onset of discomfort in the back, whereupon the extradural injection was stopped. The patient was kept recumbent for 90 min and a total of 1200 ml of Ringer lactate solution was infused. Then the patient was able to sit up and walk around with her crutches with only a minor headache. When she went home she complained of a light backache.

Thirteen days later, she presented at the emergency unit with an immobilizing backache and was admitted with suspected extradural abscess. A small degree of backache had persisted since the performance of the EBP and, 3 days before the consultation in the emergency unit, her condition worsened without any recognizable cause. She localized the backache to the lower lumbar region with radiation into the ventral side of both limbs, and into the inferior part of the abdomen. The pain was constant, but became worse with movement of the lumbar spine and eventually led to complete immobilization of the patient. She did not experience pain on coughing and did not have paraesthesiae or restricted sensory and motor function. The patient was afebrile but did have nocturnal sweating. Clinical examination showed pain on pressure and percussion in the lumbar and sacral region, which was maximal at the L5 level. In addition to distinct paravertebral myalgia, especially on the right side,

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there was restricted movement of the lumbar spine, but the remainder of the detailed neurological examination was normal. Haematological examination, including erythrocyte sedimentation rate and differentiated white blood count, was normal. Computed tomography of the lumbar spine did not indicate the presence of an abscess, or pathological alterations of the osseous structures or the discs. Lumbar myelography was normal, as were cytology and biochemical and microbiological examinations of the CSF.

The patient was mobilized with crutches and analgesic therapy and after distinct recovery occurred she was allowed home 6 days later. After 2 weeks, she no longer had back pain and had no related pain in the 12 months since then.

DISCUSSION

Accidental dural puncture occurs in 1.5–3% of attempted extradural anaesthesia [1]. Norris, Leighton and DeSimone demonstrated that identifying the extradural space when the needle bevel is orientated parallel to the longitudinal fibres significantly reduced the risk of PDPH if dural puncture occurred but, because of the large size of the needles used, PDPH is a common complication of dural puncture even with this more suitable technique [2]. When conservative treatment fails, EBP is recommended [3]. A high success rate and a low incidence of complications after EBP have made this method the treatment of choice for severe PDPH [4–6]. Although residual backache is a relatively frequent side effect of EBP [4, 6], to our knowledge an immobilizing lumbovertebral syndrome has not been described after EBP. Several factors may have contributed to this complication in our patient.

First, the reactive process in the extradural space after the injection of blood may have irritated her sensitive back. Unfortunately, little is known about the mechanisms leading to organization or resorption of an EBP or a haematoma and the metabolic products set free during this process. Samuni and colleagues have proposed a "site specific" Fenton mechanism of free radical cytotoxicity [7]. The clinical importance of this finding has been shown by Angel and co-workers in a study on the aetiological role of free radicals in haematoma-induced flap necrosis where iron or iron-bound polymers (perhaps haemoglobin) were implicated in the generation of free radicals, which may have caused tissue destruction [8]. The role of free radicals after EBP is unclear, because the aetiology of the backache seen after EBP has not been defined. In Angora goats, DiGiovanni, Galbert and Wahle found a similar tissue reaction after placement of unclotted autologuous blood in the extradural space, as was seen after diagnostic lumbar puncture [9]. However, only 2 ml of blood was injected in animals weighing up to 60 kg. Inadvertent puncture of an extradural vessel, as observed in one animal of the small control group, may lead to extravasation of a similar amount of blood. Even an extradural puncture without incident does not exclude the occurrence of a small extradural haemorrhage, as was shown in postmortem specimens of patients after continuous extradural anaesthesia [10].

Second, in so far as the large volume of blood injected into the extradural space is concerned, in an EBP study with Tc-99m labelled red blood cells, Szeinfeld and co-workers [11] found that a volume of 15 ml produced a sufficient spread of the blood in the extradural space and concluded that greater volumes [12] are not necessary and probably unwarranted. Abouleish and colleagues reported a success rate of 89% in their patients with EBP, with only 7–10 ml of blood injected [4]. Based on these studies, an injection volume of 25 ml for EBP seems, in retrospect, to be unnecessary and unwise, and this large volume may have influenced the complication in our patient.

Third, important additional factors were the unilateral plaster of Paris dressing and the difficulty of walking with crutches. It should be noted that the dramatic worsening occurred 3 weeks after mobilization of the patient, 13 days after the end of PDPH, and the patient showed a distinct recovery while still using crutches; nevertheless, we believe that the abnormal walking cannot be excluded as a significant aetiological factor for the severe backache.

In conclusion, this complication after EBP does not place into question the value of therapeutic EBP for severe PDPH. Nonetheless, it provides a note of caution and argues in favour of using smaller volumes of blood for EBP. We recommend a slow extradural injection of 15 ml or less if the patient feels radicular pain or significant back pain. If severe backache occurs after extradural or spinal anaesthesia or after EBP, urgent investigation and therapy are mandatory. Although no pathological processes were found in our patient, severe backache after extradural block should be attributed to an extradural abscess or other serious pathological process until proved otherwise.

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ACCIDENTAL SUBDURAL CATHETERIZATION: RADIOLOGICAL EVIDENCE OF A POSSIBLE MECHANISM FOR SPINAL CORD DAMAGE

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SUMMARY

We describe the inadvertent subdural insertion of a lumbar extradural catheter in a primiparous woman in labour. A small quantity of local anaesthetic resulted in extensive motor and sensory block. Computed tomography performed after contrast injection demonstrated unequivocally that the catheter was in the subdural space. The catheter and injected fluid produced considerable displacement of the arachnoid within the thecal sac. We postulate that this could result in arterial compression or direct damage to the spinal nerve roots. Such a mechanism might explain some of the cases of permanent neurological damage associated with extradural analgesia.

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural. Complications: subdural.

Accidental subdural placement of an extradural catheter is a well-described complication, although the actual incidence is not known [1–4]. Provided the extensive block produced by small volumes of local anaesthetic is recognized and any symptoms treated, full recovery may be expected. It has been suggested that a volume of fluid in the subdural space may lead to compression of the subarachnoid contents [5]. This case report demonstrates radiologically that this could easily occur.

CASE REPORT

A 21-yr-old primiparous woman was admitted to the labour suite after spontaneous rupture of membranes. Pain was managed initially with pethidine 100 mg i.m. at 02:00. By 05:30, labour had progressed to cervical dilatation of 4 cm. At this point a request was made for extradural analgesia.

The patient was 160 cm tall, of slim build (54 kg in early pregnancy) and had easily identifiable spinal features. There was no relevant past medical history. With the patient in the sitting position, a 16-gauge Tuohy needle was inserted into the L2–3 interspace, the extradural space was identified by loss of resistance to air and 0.25% plain bupivacaine 8 ml was injected through the needle. A proportion of this flowed back after the syringe was removed. At this point the patient complained of a slight frontal headache. A three-holed catheter was inserted through the needle to a depth of 4 cm within the spinal canal. Some paraesthesiae were noted in the right leg when the catheter was inserted. Another 3 ml of 0.25% bupivacaine was injected through the catheter. Satisfactory analgesia was achieved and the headache, which had been associated with slight nausea, resolved over 30 min. Although no formal assessment of the block achieved was made, the patient did not complain of excessive leg weakness and her arterial pressure remained stable.

At 07:30, after about 90 min of satisfactory pain relief, a further request for analgesia was made. The attending midwife aspirated 1 ml of clear fluid from the extradural catheter and therefore sought medical assistance. Another aspiration was negative and a 3-ml test dose of 0.125% bupivacaine with pethidine 2.5 mg ml^{-1} was given. After 20 min, pain relief was unsatisfactory, motor function was unaffected and there was no evidence of extensive block. Aspiration of the catheter was negative. A 3-ml test dose of 0.5% bupivacaine was administered. After 20 min, the patient had developed extensive leg weakness (right > left) and had bilateral pinprick analgesia to T2. Over the next 15 min she complained of tingling in the arms and fingers, heavy eyelids and sleepiness. Bilateral, marked leg weakness was present and ephedrine 12 mg i.v. was administered to treat hypotension (90/60 mm Hg). At this stage the catheter was presumed to lie in the subarachnoid space, although the repeated negative aspiration tests made subdural placement possible.

Over the next 2 h, the degree of neural block receded gradually. A healthy female infant was delivered by Ventouse extraction at 11:30. After delivery, the position of the catheter was assessed radiologically (see below) and the catheter was removed. There was full recovery of neurological

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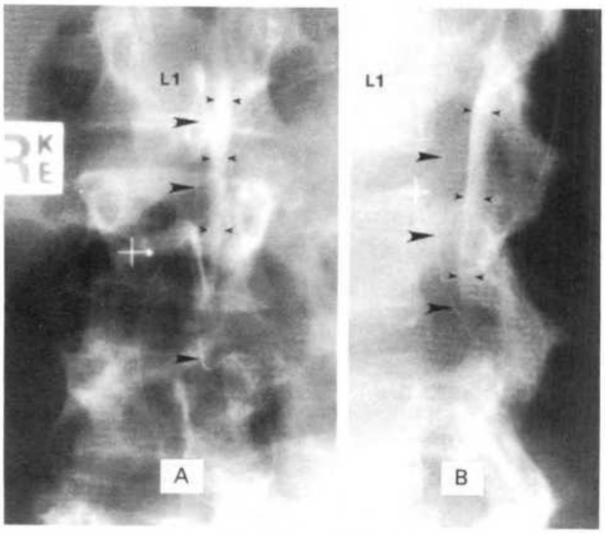

FIG. 1. Frontal (A) and lateral (B) radiographs of upper lumbal region, showing contrast-filled extradural catheter (large arrows) and contrast in the subdural space (small arrows).

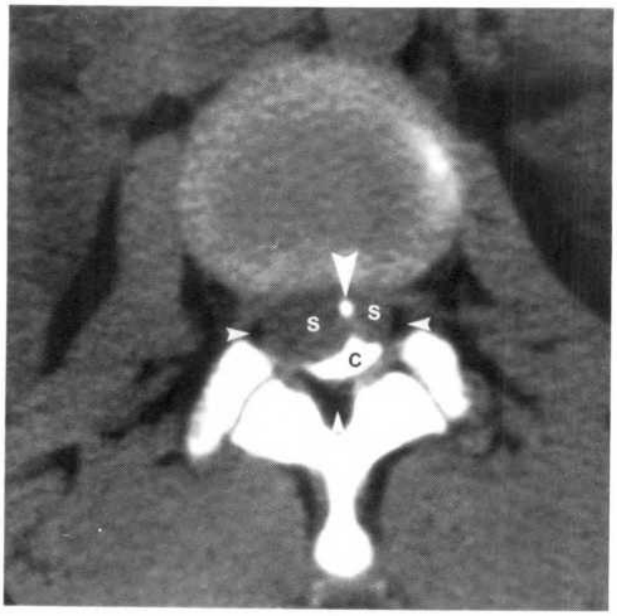

FIG. 2. Axial CT scan at the L1–2 disc level showing catheter tip (large arrow) indenting the subarachnoid space (s). The subdural contrast collection (c) has a tented appearance. The extradural space (small arrows) appears normal.

function and mother and daughter were discharged 5 days later. At no stage after delivery did the patient complain of a spinal headache.

RADIOLOGICAL FINDINGS

The range of computed tomography (CT) appearances from inadvertent subdural and extradural contrast injection during myelography have been described previously [6]. In this patient, 5 ml of the non-ionic iodinated contrast agent Iopamidol (Schering) was injected into the extradural catheter under fluoroscopic control. This was performed in the labour suite. About 1 h later, the patient was transferred to the CT scanning room, without additional injection of dye.

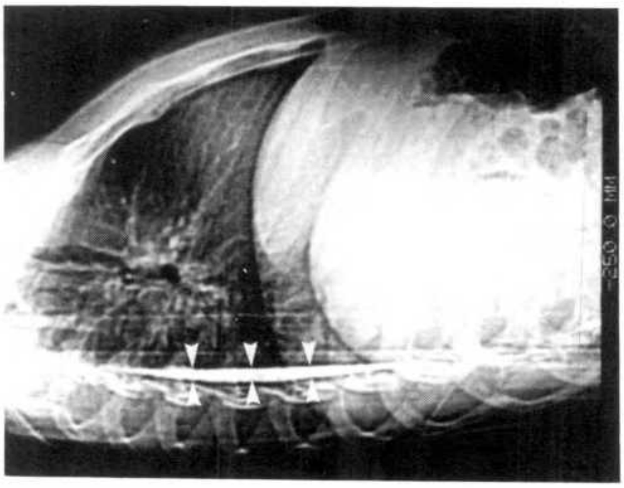

FIG. 3. Lateral CT tomogram, showing contrast layering posteriorly in the thoracic spinal canal.

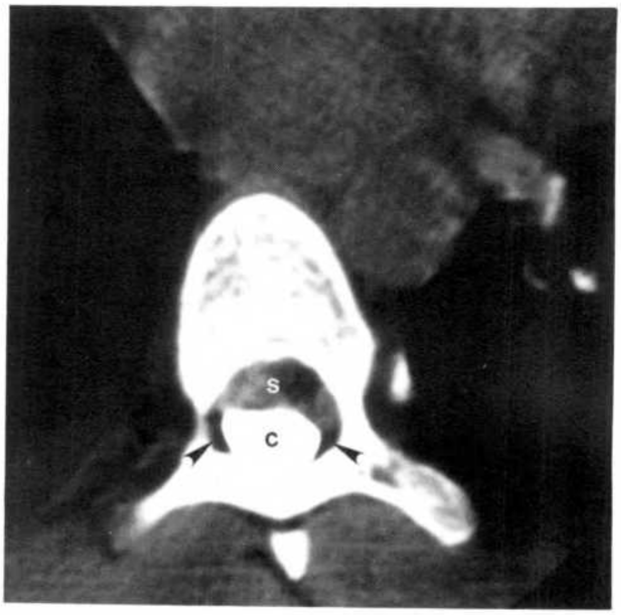

FIG. 4. Axial CT scan at T7, showing contrast (c) in subdural space displacing subarachnoid contents (s) anteriorly. The extradural space (small arrows) is intact.

The frontal radiograph (fig. 1A) showed the catheter lying close to the midline with the tip at the level of inferior endplate of L1. The lateral radiograph of the lumbar spine (fig. 1B) showed the catheter lying in a relatively anterior position within the spinal canal. Contrast was seen lying posteriorly and mainly to the left within the thecal sac. The subdural location of the catheter was confirmed by an axial CT slice at the L1–2 level (fig. 2). The catheter tip indented the arachnoid layer from the posterior direction, giving rise to a "tented" configuration of the contrast collection. A lateral CT tomogram (fig. 3) showed that much of the contrast had tracked gravitationally into the thoracic region, producing a long fluid level within the spinal canal. The subdural location of the contrast was also demonstrated by a single axial CT slice at the level of greatest dependency at T7 (fig. 4). The spinal cord, within the subarachnoid space, was displaced anteriorly and of normal density. The extradural fat planes were intact, outlining the outer margins of the thecal sac. No contrast was seen in the extradural space.

DISCUSSION

This case report demonstrates the difficulties associated with identification of the extradural space. The only possible clue to abnormal placement on insertion was the frontal headache experienced on injection of bupivacaine through the needle. It is possible that CSF may have been displaced intracranially to cause symptoms of a high pressure headache. Williamson [7] reported a severe frontal headache which persisted for several days after inadvertent subdural injection of a steroid mixture.

Abnormal placement was suspected after the test dose of 0.5% bupivacaine. The extensive block produced was unlikely to have been caused by extradural insertion. Assessment of the block height was made only after the catheter was thought not to be in the extradural space. It is possible that, if no local anaesthetic were given "through the needle" at the start of the procedure and a test dose of bupivacaine were given via the catheter followed by careful assessment of the level of the block, the misplacement may have been identified sooner. The failure of the weaker solution of bupivacaine to produce evidence of catheter position demonstrates the importance of using an appropriate concentration when using a test dose—that is, one that should produce unequivocal symptoms and signs.

Collier [8] described the clinical indicators of subdural injection, notably: moderate hypotension, onset of symptoms from 15 to 30 min, progressive respiratory depression and complete recovery after 2 h. In this patient, there were no respiratory problems. The complaint of heavy eyelids and the observation of small pupils could be related to Horner's syndrome, although the small quantity of pethidine (7.5 mg) injected beforehand may have contributed to the miosis. There was no complaint of nasal congestion.

One of the peculiar aspects of this case was the aspiration of 1 ml of clear fluid before the top-up dose was to be injected. Given that the catheter was demonstrated to be subdural, this fluid was probably the remainder of the initial injection of bupivacaine. A negative catheter aspiration test does not exclude subarachnoid placement, as the catheter could kink or the filter may not permit free retrograde flow. On this occasion, it was the positive aspiration test that alerted staff to there being a malposition of the catheter. In a case reported previously [9], clear fluid was aspirated from a catheter thought to be subdural; however, the fluid was not tested and the catheter position not confirmed.

As illustrated by the CT scan, the 5 ml of injected contrast medium represented a significant space-occupying mass within the thecal sac. If a large volume of local anaesthetic liquid were injected into the space, it is possible that pressure could be exerted on the spinal nerve roots or on the cord itself. Alternatively, compression of spinal vessels could lead to ischaemia. Both mechanisms could result in neurological damage. After the local anaesthetic diffused out of the space, there would be no evidence of the cause. This may explain some of the rare causes of permanent neural damage after an apparently straightforward extradural anaesthetic. While the exact volume required to cause damage is a matter for conjecture, the 5 ml of contrast administered in this patient does seem to be occupying a considerable volume within the spinal canal.

In summary, this case report demonstrates the occurrence of subdural insertion of an extradural catheter. Identification of subdural placement is difficult, but should always be considered if a more extensive block occurs than would normally be expected with a given dose of local anaesthetic. This case emphasizes the importance of having appropriately trained staff in attendance or immediately available at all times when managing extradural analgesia. A high index of suspicion should be maintained if any abnormal symptoms or signs are reported.

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LIFE-THREATENING ACUTE RESPIRATORY DISTRESS IN LATE PREGNANCY

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SUMMARY

Acute severe ventilatory failure from any cause is always a critical emergency. In advanced pregnancy, such an episode is particularly hazardous. The management of a pregnant patient who presented with an acute episode of respiratory distress is described. Although this was thought initially to be an asthmatic attack, there was evidence of upper airway obstruction caused by an enlarged thyroid. The major complicating factors and aetiology are discussed.

KEY WORDS

Airway: obstruction. Complications: acute ventilatory failure. Pregnancy.

CASE REPORT

The duty anaesthetists were forewarned of a patient *en route* to the emergency department. She was a 28-yr-old at term in her third pregnancy with a history of asthma, and presenting in severe respiratory distress.

On arrival, she was severely dyspnoeic with marked cyanosis and tachycardia, but with a good pulse pressure and peripheral perfusion. She appeared awake, but was unresponsive. Although little air entry could be heard, there was a wheeze, which was more marked on expiration than inspiration. She was given oxygen and salbutamol by nebulizer and i.v. infusion. A left lateral tilt was maintained to avoid aorto–caval compression. The fetal heart rate was normal. Arterial blood-gas analysis (which was not received until some time later) showed pH 6.82, Pa_{O_2} 6.0 kPa, Pa_{CO_2} 14.6 kPa, base excess -22 mmol litre^{-1} and Sa_{O_2} 42%.

A brief history was obtained from the husband, who confirmed a past history of asthma, with recent problems strongly suggestive of an acute asthmatic attack. There was also a 2- or 3-yr history of mild nodular thyroid enlargement.

As the patient's condition did not improve immediately with bronchodilator therapy, because of the severity of her respiratory distress we proceeded to tracheal intubation and assisted ventilation without further delay. It was now noted that there was a moderately enlarged thyroid which interfered with the application of cricoid pressure. Anaesthesia was induced with etomidate 6 mg and tracheal intubation was facilitated by suxamethonium 100 mg. The mouth, pharynx and glottis were normal, in particular there was no laryngeal oedema, and the tracheal tube passed easily and without obstruction.

The lungs were easy to ventilate and the cyanosis resolved rapidly, excluding an acute asthmatic attack. The thyroid seemed to be larger. There was now fetal bradycardia and, as the mother's condition had been stabilized, arrangements were made for delivery by Caesarean section and an ENT surgeon was called. A live male infant was delivered; tracheal intubation and artificial ventilation were required.

During the Caesarean section the thyroid continued to expand in size and an ultrasound scan was performed in the theatre; this demonstrated an enlarged thyroid containing a cystic mass. Surgical exploration confirmed an enlarged thyroid with massive expansion of the isthmus, some retrosternal extension and relative sparing of the upper poles. After subtotal thyroidectomy, it was found that the isthmus contained a large haemorrhage. Tracheotomy was performed as there was a degree of tracheomalacia. Direct laryngoscopy confirmed normal mouth and pharynx, and glottis.

After a short period of ventilation in the Intensive Care Unit, spontaneous ventilation was re-established and the patient regained full consciousness with no neurological deficit. The tracheostomy was closed on the 5th day and the patient was discharged home later. On review in outpatients clinics, she was continuing to make a good recovery. The tracheostomy had healed and there has been no further dyspnoea.

Unfortunately, the baby showed evidence of hypoxic brain damage. A scan showed several intracranial bleeds and he died on the 3rd day after operation.

DISCUSSION

This patient presented *in extremis*, so only an extremely limited history was immediately available and this strongly indicated a severe asthmatic attack;

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clinical examination was compatible with this diagnosis. Our initial treatment was directed, therefore, at treating an asthmatic attack and the correct treatment to relieve her airways obstruction was delayed. She failed to respond rapidly to pharmacological treatment and so the trachea was intubated in the emergency department within a few minutes of her arrival.

Had it been possible to question the patient, we would probably still have been misled. After operation, she recalled that she had felt a tightness in her chest, similar to an early asthmatic attack (similar indeed to one she had had the previous week). She denied any abnormal symptoms such as dysphagia. The dyspnoea increased rapidly and she was taken via the general practitioner's surgery to hospital with minimal delay, during which time she lost consciousness. Two years previously, she had developed a small benign multicystic goitre, but no intervention was required. There had been no further thyroid enlargement noted at the antenatal booking clinic or when she was visited at home the day before admission, by a midwife who knew her well. Interestingly, her mother had required a thyroid operation about a year previously and had undergone tracheotomy. There had been no symptoms or signs of toxaemia of pregnancy, or of any other cause of laryngeal oedema.

The aetiology of this event remains rather obscure. Although the history indicated asthma, the operative finding was of an acute expansion of an already enlarged thyroid as a result of haemorrhage. There are several possible explanations.

First, the acute expansion, particularly of the thyroid isthmus, may have compressed the trachea, causing obstruction. The trachea was rather soft and the bulk of the haematoma was in the isthmus. This sequence is supported by the surgical evidence, but not by the history. A previous report of tracheal obstruction by an enlarged thyroid had an associated clear history of goitre, dysphagia and dyspnoea [1]. It is interesting that the tracheal tube passed the obstruction so easily, and that the thyroid was only moderately enlarged when the patient was first seen in hospital.

Second, the acute swelling of the isthmus might have increased the pressure caused by the retrosternal extension of the gland, resulting in obstruction at this point. This would explain why the symptoms and signs suggested an intrathoracic problem. However, at operation the retrosternal component did not appear significant.

Third, it may be that the initial event was an acute asthmatic attack which was compounded by tracheal obstruction caused by tracheomalacia, and that this episode triggered bleeding into the nodular goitre. This more complex sequence provides a fuller explanation of the clinical picture.

There was no hypertension and no oedema obvious on tracheal intubation, so it seems unlikely that toxaemia of pregnancy was a significant contributory factor.

Tracheomalacia is a well recognized cause of acute airway obstruction. There is a previous report in which this appears to have resulted in a clinical picture resembling asthma in a pregnant patient [2]. In that case, a massive goitre had been excised some years before.

Both asthma and thyroid disease may exist during pregnancy, and both may be affected by pregnancy. Asthma tends to exhibit a small overall improvement, but there is considerable individual variability [3]. It has been estimated that a life-threatening attack of asthma may be expected in 0.05–0.2% of all pregnancies [4].

Pregnancy has a goitrogenic effect. Part of this increase in thyroid size is caused by the increased body mass, but hormone concentrations are increased also [5]. In a review of a large series of patients presenting for thyroid surgery, 2% had significant respiratory compromise before operation, and 0.76% had severe dyspnoea resulting in episodes of suffocation, or of permanent dyspnoea with cyanosis [6]. Another group reported 24 patients requiring emergency admission caused by life-threatening airway distress resulting from thyroid disease over a 4-yr period; nine of the patients needed immediate tracheal intubation and two were in the last trimester of pregnancy [7].

In most cases of respiratory obstruction caused by an enlarged thyroid, the symptoms are long standing and include feelings of pressure and dysphagia, in addition to dyspnoea. However, haemorrhage into a nodule may occur at any time, causing acute symptoms [8].

This case serves as a reminder that most medical emergencies may also occur during pregnancy, which further complicates the management. The true cause of an emergency may not be immediately obvious.

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CORRESPONDENCE

MIDAZOLAM AND CARDIOVERSION

Sir,—We read with interest the article by Fennelly and others [1], and wish to report our own experience, which is different in some respects. The main difference between their study and ours [2] was that the dose of midazolam we used was much greater in order to induce anaesthesia (and not sedation). Although benzodiazepines are known to cause anterograde amnesia, Krichbaum and Hamid [3] reported a few patients who were aware during cardioversion under midazolam sedation. Our own experience was that the anaesthesia produced by midazolam, in a much greater dose, was poor because many patients had flexion movements of the arms and legs and some needed to be restrained. Flumazenil clearly reversed the effect of midazolam, but many patients were resedated at the time of interview 4 h later. Also, the statement that this was "the first specific report of the use of midazolam, reversed by flumazenil, for anaesthesia for cardioversion" is incorrect, as both the above studies [2, 3] have examined midazolam sedation for cardioversion. Although the purpose of the present study was not to evaluate the usefulness of midazolam as an anaesthetic for cardioversion, we think that it is important for the reader to know that midazolam is not the best choice for this procedure, even though it can be reversed effectively by flumazenil.

A. Gupta
M. Vegfors
C. Lennmarken
Linköping

1. Fennelly ME, Powell H, Galletly DC, Whitwam JG. Midazolam sedation reversed with flumazenil for cardioversion. *British Journal of Anaesthesia* 1992; **68**: 303–305.
2. Gupta A, Lennmarken C, Vegfors M, Tyden H. Anaesthesia for cardioversion: a comparison between propofol, thiopentone and midazolam. *Anaesthesia* 1990; **45**: 872–875.
3. Krichbaum DW, Hamid I. Midazolam sedation and amnesia in elective cardioversion. *Clinical Pharmacy* 1988; **7**: 423.

DELAYED SEPTICAEMIA AFTER EXTRADURAL STEROID TREATMENT

Sir,—Further to the recent case report of a delayed complication after extradural steroid therapy [1], we wish to report a life-threatening event associated with extradural steroid administration.

A female of 54 yr was referred to the Pain Clinic for management of lower back pain which had been present for 9 months without improvement on conservative treatment. The pain radiated posteriorly to the left foot, was exacerbated by exercise and was restricting activity. The patient was generally well; she smoked 15 cigarettes per day, but denied respiratory symptoms. On examination, the single abnormal sign was limited straight leg raising on the left. Lumbar spine x-rays showed degenerative changes, particularly at the L4-5 region. A lumbar extradural injection of methyl prednisolone 120 mg (Depo-Medrone) was performed using a strict aseptic technique.

Nine days later, the patient began to notice a non-productive cough and became dyspnoeic; rigors developed and the following day she was admitted to hospital, where she was found to have pyrexia (temperature 39.9 °C), tachycardia and mild neck stiffness. Clinical signs of consolidation in the right chest were confirmed by chest x-ray. She became hypotensive (systolic arterial pressure 70 mm Hg) and required resuscitation with i.v. fluids. A diagnosis of septicaemia secondary to a chest infection was made. Investigations revealed haemoglobin 134 g litre^{-1}, white blood cells 21.8×10^9 litre^{-1}, with normal biochemistry; lumbar puncture was normal; blood and urine cultures subsequently were negative; no sputum could be obtained. I.v. cefuroxime and erythromycin therapy was initiated, the patient's condition improved rapidly and she was discharged home 6 days later.

We consider that this patient's admission was precipitated by two factors: immunosuppression secondary to the steroid therapy and cigarette smoking. Steroids have been administered by the extradural route for 40 yr [2] and the technique is considered to be safe in experienced hands. Local adverse effects, particularly haematoma [3], abscess [1, 4] and bacterial meningitis [5], are well described, but systemic effects are often not considered and two major reviews of extradural steroid therapy discussed septicaemia without the presence of extradural abscess [6, 7].

Steroids depress the immune system via several routes [8]. Lymphopaenia affecting particularly the T helper cells occurs as the lymphocytes are sequestered into bone marrow; the resting macrophages are inhibited because of reduction in complement and IgG receptors; antigen handling by macrophages is impaired, leading to a poor primary antibody response; neutrophils fail to be exported into tissues. The effects of "depo" preparations can be shown to persist for up to 3 weeks [9].

We suggest therefore, that any patient receiving a depo preparation of steroid should be advised to seek medical advice at the earliest symptom of possible infection, and that medical staff should be aware of the possibility of late septicaemia.

R. H. Elliott
B. J. Collett
Leicester

1. Sowter MC, Burgess NA, Woodsford PV, Lewis MH. Delayed presentation of an extradural abscess complicating thoracic extradural analgesia. *British Journal of Anaesthesia* 1992; **68**: 103–105.
2. Robecchi A, Capra R. L'idrocortisone (composto F). Prime esperienze cliniche in campo reumatologico. *Minerva Medica* 1952; **2**: 1259–1263.
3. Williams KN, Jackowski A, Evans PJD. Epidural haematoma requiring surgical decompression following repeated cervical epidural steroid injections for chronic pain. *Pain* 1990; **42**: 197–199.
4. Shealy CM. Dangers of spinal injections without proper diagnosis. *Journal of the American Medical Association* 1966; **197**: 1104–1106.
5. Dougherty JH, Frazer RA. Complications following intraspinal injections of steroids. *Journal of Neurosurgery* 1978; **48**: 1023–1025.
6. Kepes ER, Duncalf D. Treatment of backache with spinal injections of local anesthetics, spinal and systemic steroids. A review. *Pain* 1985; **22**: 33–37.
7. Benzon HT. Epidural steroid injections for low back pain and lumbosacral radiculopathy. *Pain* 1986; **24**: 277–295.
8. Chapel H, Haeney M. *Essentials of Clinical Immunology*, 2nd Edn. Oxford: Blackwell Scientific Publications, 1988; 135–136.
9. Burn JM, Langdon L. Duration of action of methyl prednisolone. A study in patients with the lumbosciatic syndrome. *American Journal of Physical Medicine* 1974; **53**: 29–34.

Sir,—We are grateful for the opportunity to comment on the letter of Elliott and Collett, in response to our report [1]. They report a case of septicaemia following extradural administration of steroids for the relief of back pain which is not comparable to our own. Ours was a thoracic administration, analgesics were administered and our patient developed a local septic complication. We would, however, take issue with the authors.

We would agree that smoking was a factor in the development of a chest infection in their patient, but dispute the importance of the extradural steroids. The small dose of methyl prednisolone administered (120 mg) into the extradural space would seem unlikely to be sufficient to cause generalized immunosuppression. Certainly, it is much smaller than that administered i.v. for therapeutic immunosuppression. In contrast, our patient was immunosuppressed by rheumatoid arthritis and the administration of long-term high-dose immunosuppressive drugs. This is seen in the white cell response to infection — 6.8×10^9 litre^{-1} in our patient, but 21.8×10^9 litre^{-1} in theirs.

In summary, therefore, we welcome the interest shown by Elliott and Collett, but feel that their patient suffered as a consequence of smoking, rather than of their intervention.

M. W. Scriven
N. A. Burgess
P. W. Woodsford
M. H. Lewis
Glamorgan

1. Sowter MC, Burgess NA, Woodsford PV, Lewis MH. Delayed presentation of an extradural abscess complicating thoracic extradural analgesia. *British Journal of Anaesthesia* 1992; **68**: 103–105.

STEROID THERAPY AND EXTRADURAL ANALGESIA

Sir,—I read with interest the case report of Dr Sowter and colleagues [1] describing the delayed presentation of an extradural abscess in a patient with rheumatoid arthritis who had been receiving steroids, and the letter by McQuay and Jadad [2] who have criticized as premature the suggestion that extradural techniques should be contraindicated in such patients. McQuay and Jadad base their criticism on the observation that this is but a single case; furthermore, they comment that there have been no cases of delayed extradural abscess in patients receiving steroids by the extradural route for the management of chronic back pain and that there have been no reports of extradural abscesses in cancer patients taking oral steroids who receive extradural therapy.

In fact there have been reports of extradural abscesses occurring after administration of extradural steroids for back pain and an extradural abscess has occurred in a patient who was taking oral steroids but did not have cancer. Chan and Leung [3] described a diabetic patient who developed an extradural abscess after a single extradural injection of triamcinolone acetonide for sciatica. Similarly, Goucke and Graziotti [4] described a patient who developed an extradural abscess 3 weeks after receiving a course of three extradural injections of methylprednisolone and local anaesthetic for chronic back pain. Strong [5] described delayed presentation of an extradural abscess after placement of extradural catheters in two patients who received steroids; the first patient suffered from herpes zoster and received extradural methylprednisolone, the second patient suffered from reflex sympathetic dystrophy and had been receiving oral prednisone.

McQuay and Jadad also refer to a case of an iatrogenic extradural abscess that occurred in a patient 9 days after removal of an extradural catheter, suggesting Dr Sowter's paper to be the third report of extradural abscess with delayed presentation. In fact there have been several other reports of iatrogenic extradural abscesses with delayed presentation which have occurred up to 5 months after placement of extradural catheters [5–7].

It is debatable if concurrent steroid use should be a contraindication to extradural therapy. However, it seems prudent to urge caution whenever a patient is receiving steroids or when steroids are to be administered extradurally. The risk and benefit must be considered, informed consent obtained, scrupulous attention given to aseptic technique, and the patient must be carefully followed up to check for signs of complications.

W. D. Ngan Kee
Wellington, New Zealand

1. Sowter MC, Burgess NA, Woodsford PV, Lewis MH. Delayed presentation of an extradural abscess complicating thoracic extradural analgesia. *British Journal of Anaesthesia* 1992; **68**: 103–105.
2. McQuay HJ, Jadad AR. Is steroid therapy a contraindication to extradural analgesia? *British Journal of Anaesthesia* 1992; **68**: 540–541.
3. Chan ST, Leung S. Spinal epidural abscess following steroid injection for sciatica. *Spine* 1989; **14**: 106–108.
4. Goucke CR, Graziotti P. Extradural abscess following local anaesthetic and steroid injection for chronic back pain. *British Journal of Anaesthesia* 1990; **65**: 427–429.
5. Strong WE. Epidural abscess associated with epidural catheterization: A rare event? Report of two cases with markedly delayed presentation. *Anesthesiology* 1991; **74**: 943–946.
6. Sollmann WP, Gaab MR, Panning B. Lumbar epidural hematoma and spinal abscess following peridural anesthesia. *Regional Anesthesie* 1987; **10**: 121–124.
7. Reynolds PC, Hahn MB. Early diagnosis of a spinal epidural abscess. *Regional Anesthesia* 1991; **16**: 47–58.

INSULATED REGIONAL BLOCK NEEDLES

Sir,—As a regular user of insulated needles, I was very interested to read the article by Jones, De Jonge and Smith [1] on the use of uninsulated needles in local anaesthetic blocks. However, one of the basic premises of their article seems to be at odds with general perceptions. I refer to the unreferenced statements that "the form...of the voltage field surrounding the needle...is important", and "the nerve is most likely to be stimulated when it lies within a steep voltage gradient." In support of this they stated that a reduction of the transmembrane potential to a value of 55 mV generates a spike potential, and that this can be achieved by movement of ions caused by a potential gradient in the area of the nerve. It is not immediately obvious to me how a movement of ions *per se* (i.e. current) would reduce the transmembrane potential. A major factor in the determination of the transmembrane potential is, however, the absolute voltage surrounding the nerve, and it may be this, rather than its gradient, that is the important measure. Indeed, in a previous work on the subject, Bashein, Haschke and Ready [2] referred to zones of depolarization with reference to their potential, rather than to their potential gradient.

The fact that stimulation of a nerve is more reproducible with a given current through the needle than with a given potential difference between it and the earth electrode may be explained by the fact that there is a variable resistance in the area of the earth electrode itself. If the needle is embedded in extracellular fluid, the resistance characteristics around it are unlikely to vary much between sites or even between patients: extracellular fluid has a constant composition. (The search for nerves embedded in fat may be a different matter.) Achieving a constant current would therefore produce a constant pattern of potentials around the needle.

Development of this line of reasoning would refute the conclusions of Jones, De Jonge and Smith that an insulated needle would be as likely to fire a spike potential in a nerve that lay significantly in front of or behind the tip as it would be if the tip were adjacent to the nerve, and that in the case of an uninsulated needle, stimulation would occur only if the needle (I presume they mean the *tip* of the needle) is within 2 mm of the nerve. I agree that the steep diminution of potential in front of an insulated needle results in a more accurate localization of the nerve as the needle approaches it, but I suggest that this would be offset by a lower accuracy of localization when the needle has been advanced so that the nerve lies to the side of the needle.

M. S. Read
Montpellier

1. Jones RP, De Jonge M, Smith BE. Voltage fields surrounding needles used in regional anaesthesia. *British Journal of Anaesthesia* 1992; **68**: 515–518.
2. Bashein G, Haschke RH, Ready LB. Electrical nerve location: numerical and electrophoretic comparison of insulated *vs* uninsulated needles. *Anesthesia and Analgesia* 1984; **63**: 919–924.

Sir,—We are grateful for the opportunity to respond to the letter from Dr Read, and agree with the final summarizing statement. We feel that such conclusions confirm the statement of Pither, Raj and Ford that "while both types of needle have their advocates, knowledge of their electrical behaviour enables both to be used effectively" [1].

However, we are at a variance with the reasoning that leads to the final statement. On the basis of the electrophysiology of nerve conduction [2], we believe that it is the voltage gradient across the nerve membrane (transmembrane potential) that determines the conduction state of a nerve. "Zones of depolarization" is a term used by Bashein, Haschke and Ready [3], but the term is not defined clearly and the plots used in their computer simulation represent contours of constant field magnitude based on mathematical models in communication electronics. In our experimental model, we attempted to create conditions that were more physiological although, as Dr Read points out, the model does not allow for tissues of different electrical conductivity such as bone and fat.

In a clinical situation, a choice of either insulated or uninsulated needles may be made provided that the pattern of stimulation as the needle approaches the nerve is recognized by the user. Other factors may determine the choice of needle, such as tip design and cost.

R. P. Jones
Redditch

1. Pither CE, Raj PP, Ford DJ. The use of peripheral nerve stimulators for regional anesthesia: a review of experimental characteristics, technique, and clinical applications. *Regional Anesthesia* 1985; **10**: 49–58.
2. Guyton AC. *Textbook of Medical Physiology*, 8th Edn. Philadelphia: W. B. Saunders, 1991; 51–66.
3. Bashein G, Haschke RH, Ready LB. Electrical nerve location: numerical and electrophoretic comparison of insulated *vs* uninsulated needles. *Anesthesia and Analgesia* 1984; **63**: 919–924.

EFFECT OF PREOPERATIVE OPIOID ADMINISTRATION ON POSTOPERATIVE PAIN

Sir,—We read with considerable interest the study on pre- *vs* postoperative block [1]. The study evaluated the effects of a local anaesthetic inguinal field block administered before or after inguinal herniorrhaphy on postoperative pain and analgesic consumption. Based on the results of animal studies which demonstrate that pretreatment with mu opioid receptor agonists [2, 3] or local anaesthetic agents [4] prevents development of injury-induced spinal hyperexcitability [2, 3] and pain related behaviour [4], one would have expected pain to be more intense among patients who received the block after operation.

The authors discussed two factors in an attempt to explain the negative findings: that incomplete peripheral block or C-fibre activity resulting from wound inflammation in the postoperative period may have induced a state of CNS sensitization in both groups, resulting in non-significant differences in postoperative pain intensity and analgesic consumption. The authors' discussion of the negative findings is based on the assumption that CNS sensitization occurred in both groups. We wish to draw attention to two related issues that also may explain the negative findings, but from the perspective that CNS sensitization did not occur in either of the groups.

The first issue concerns the authors' use of peroperative opioids. In addition to i.v. thiopentone, all patients received an opioid–nitrous oxide–oxygen anaesthetic technique, including administration of at least 10 μg kg^{-1} of alfentanil before incision. The total amount may have been as great as 15 μg kg^{-1}, but the exact timing of the additional 5 μg kg^{-1} relative to the time of incision is not made explicit in the text. Nevertheless, it is likely that this dose of alfentanil provided a sufficient block of central nociceptive activity and thus prevented or attenuated the development of CNS sensitization in all patients—even if the inguinal field block had been incomplete. This possibility is supported by a recent study [5] in which a loading dose of alfentanil 15 μg kg^{-1} i.v. was sufficient to reduce *already established* postoperative pain from a VAS score of 8.0 to a score of 0.1 in less than 5 min.

Animal studies [2] have shown that the dose of systemic morphine required to *abolish* established noxious stimulus-induced central hyperactivity is an order of magnitude greater than that required to *prevent* these prolonged central consequences when administered before injury. Taken together, these findings support the suggestion that, in the study by Dierking and colleagues, the afferent barrage was attenuated in all patients before operation.

The second issue concerns the overall magnitude of postoperative pain. The very low level of postoperative pain demonstrated in this study is an admirable achievement and reflects earlier work from this group [6]. However, it would be very difficult to demonstrate an advantage of pre- *vs* postoperative analgesia when pain intensity is low and outcome measures depend on finding between-group differences in pain or postoperative analgesic use. For example, median VAS scores at rest were so low in the postoperative inguinal field block group (median < 10 mm), that it would be virtually impossible to demonstrate an improvement in analgesia from any therapeutic intervention.

If a state of CNS sensitization had been induced in both groups, one would have expected greater pain scores, greater morphine consumption, or both, as the implications of the experimental evidence [7] include hyperalgesia and allodynia. However, morphine intake and pain remained relatively constant over time, so it does not appear that CNS sensitization was induced after the action of lignocaine had disappeared. We offer the suggestion that the small VAS scores and small requirements for morphine in both groups reflect an attenuation of the central consequences of the afferent barrage brought about by the combined effects of the systemic opioid (administered before operation) plus regional local anaesthetic. The authors may have accomplished in both groups that which they had intended in only the preoperative inguinal field block group.

J. Katz
B. P. Kavanagh
A. N. Sandler
Toronto, Canada

1. Dierking GW, Dahl JB, Kanstrup J, Dahl A, Kehlet H. Effect of pre- *vs* postoperative inguinal field block on postoperative pain after herniorraphy. *British Journal of Anaesthesia* 1992; **68**: 344–348.
2. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. *Neuroscience Letters* 1986; **64**: 221–225.
3. Dickenson AH, Sullivan AF. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
4. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research* 1990; **535**: 155–158.
5. Camu F, Debucquoy F. Alfentanil infusion for postoperative pain: A comparison of epidural and intravenous routes. *Anesthesiology* 1991; **75**: 171–178.
6. Dahl JB, Rosenberg J, Dirkes WE, Mogensen T, Kehlet H. Prevention of postoperative pain by balanced analgesia. *British Journal of Anaesthesia* 1990; **64**: 518–520.
7. Woolf CJ. Recent advances in the pathophysiology of acute pain. *British Journal of Anaesthesia* 1989; **63**: 139–146.

Sir,—We appreciate the interesting comments made by Katz, Kavanagh and Sandler on our paper [1]. They suggest that the negative findings may be explained by the preoperative administration of alfentanil and that the low level of postoperative pain made it impossible to demonstrate an improvement in analgesia from any therapeutic intervention. However, we do not agree with this interpretation. First, postoperative pain was not, as suggested, constant over time (figures 2 and 3 in [1]). On the contrary, a considerable and statistically significant ($P < 0.05$) increase in pain VAS during mobilization and cough was observed from 1 to 4 h after surgery in patients receiving *preoperative* block, and from 1 to 6 h in patients receiving *postoperative* block. Thus postoperative pain was not *prevented* by preoperative alfentanil (and inguinal field block in the pre-block group) and CNS sensitization may have been induced in both groups of patients during or after surgery. This is in agreement with the only available prospective controlled clinical study on the effect of perioperative i.v. alfentanil on postoperative pain after surgery, in which no reduction in the need for postoperative opioids was demonstrated in patients receiving a preoperative bolus of alfentanil 30 μg kg^{-1} followed by an intraoperative infusion of alfentanil 40 μg kg^{-1} h^{-1}, compared with placebo [2]. The study by Camu and Debucquoy [3] is not relevant to this discussion, as it only demonstrated a fast pain relieving effect of alfentanil, but because of its short duration of action a continuous administration was used subsequently.

Second, inguinal field block provided effective pain relief during rest, but most patients experienced significant pain during relevant physical activity. Mean (SD) VAS during mobilization and cough 6 h after surgery in the post-block group, when the action of lignocaine would have disappeared, was 26 (17) mm and 44 (21) mm, respectively. As a reduction in VAS of 1 SD was considered to be the smallest clinically relevant difference, the power of the study is 80–85% at the 5% significance level. We consider this to be acceptable and found no significant differences between the groups.

In conclusion, postoperative pain was not prevented by preoperative alfentanil in either of the study groups. Therefore, we maintain that our study does not support the suggestion that pre-emptive analgesia with a conventional inguinal field block is of clinical importance compared with a similar block administered after operation.

J. B. Dahl
H. Kehlet
G. Dierking
A. Dahl
J. Kanstrup
Copenhagen and Silkeborg, Denmark

1. Dierking G, Dahl JB, Kanstrup J, Dahl A, Kehlet H. The effect of pre- *vs* postoperative inguinal field block on postoperative pain following herniorrhaphy. *British Journal of Anaesthesia* 1992; **68**: 344–348.
2. Koskinen R, Tigerstedt I, Tammisto T. The effect of peroperative alfentanil on the need of immediate postoperative pain relief. *Acta Anaesthesiologica Scandinavica* 1991; 35 (Suppl. 96): 21.
3. Camu F, Debucquoy F. Alfentanil infusion for postoperative pain: A comparison of epidural and intravenous routes. *Anesthesiology* 1991; 75: 171–178.

DAMAGE TO COAXIAL BREATHING SYSTEMS

Sir,—The letter by Williams and Van Hasselt [1] drew attention to the need for appropriate safety checks before using the Bain anaesthetic system. Their reference to the "Bain" system refers probably to the coaxial modification produced by several manufacturers rather than to Bain's original design, which had the central hose entering through the side of the outer hose rather than connected to a centre inner mount. One would expect Bain's original design, although not as neat, to be less vulnerable to the type of failure described.

They referred to the problem as an infrequently encountered complication. It is my belief that this is a far more frequent problem than is appreciated. I have discovered one seriously faulty Penlon Coaxial D circuit myself whilst checking an anaesthetic machine before use and have first hand knowledge of several other episodes involving a coaxial D system central hose disconnection or inner mount fracture.

The faulty circuit I discovered had a bent inner mount which had fractured. On investigation, it was found that the coaxial D system had been left connected to the anaesthetic machine the previous evening and had remained connected when the machine was moved out of theatre overnight and returned to theatre the following morning. The anaesthetic machine had a fixed common gas outlet rather than one mounted on a swivel. The most likely explanation of the damage was that the coaxial D system caught on a doorway or other obstacle while the machine was being moved. Presumably, circuits mounted upon anaesthetic machines which lack a swivel connection are at greater risk of damage by this mechanism.

In addition to checks for detecting faulty equipment before use, there is a need for appropriate measures to prevent damage. These should include disconnection of breathing systems from the common gas outlet when not in use. This is particularly important when the machine is being moved from one location to another.

M. W. D. Liddle
Coventry

1. Williams AR, Van Hasselt G. Adequacy of preoperative safety checks of the Bain breathing system. *British Journal of Anaesthesia* 1992; **68**: 637.

Sir,—Thank you for the opportunity to reply to Dr Liddle's letter. As he correctly infers, reference to the "Bain" circuit did refer to the coaxial modification of the original Bain breathing system.

We referred to defects of the inner fresh gas flow tube as an infrequently encountered complication, and this represents our own experience. Dr Liddle believes this problem is far more frequent than is commonly appreciated. Perhaps we should have stated that it was an infrequently *reported* complication.

A. R. Williams
Poole, Dorset

UNNECESSARY PREOPERATIVE INVESTIGATIONS IN CHILDREN

Sir,—Following an editorial in the *Canadian Journal of Anaesthesia* [1] entitled "Screening Tests Before Surgery in Children", we have audited our own practice at the Sheffield Children's Hospital day unit.

All of our day-case general surgical patients have routine preoperative haemoglobin (Hb) measurement as in most of the Canadian centres, but contrary to practice in many British Children's Hospitals. We undertook a 3-month prospective and 9-month retrospective study of Hb results and reasons for cancellation. Our results reiterated the Canadian experience, in that over the 12-month period no child's admission was cancelled because of unexpected anaemia and only two children were found to have an Hb < 10 g dl^{-1}. One of these children was found to have an Hb of 8.7 g dl^{-1}, but had a history of rectal bleeding and therefore required a preoperative Hb assessment before colonoscopy; the other had an Hb of 9.9 g dl^{-1} and had their admission cancelled because of a cold. The remainder of the children were found not to be anaemic and the results were within a normal distribution. Even children in the so-called dilutional anaemic stage of 2–6 months had values > 10 g dl^{-1}, but this raises the question; are we looking for values of less than 10 g dl^{-1}, or should we be looking for pathological anaemia?

In view of these findings, we have now changed our practice such that, in children older than 2 yr, a preoperative measurement of Hb is performed only if there is a specific indication—suspected haemoglobinopathy or symptoms or signs suggestive of anaemia.

In children younger than 2 yr, we have at present continued to test the Hb before operation, although our audit did not indicate this to be necessary. It was felt that, in this age group, symptoms and signs of anaemia were unreliable and preoperative screening may represent the first opportunity for analysis, although this is subject to review. We hope our experience may influence units still routinely testing all day-case surgical children, as the saving both in financial terms and unnecessary stress to children and parents is considerable.

A. Wilson
N. Pereira
Sheffield

1. Steward DJ. Screening tests before surgery in children. *Canadian Journal of Anaesthesia* 1991; **38**: 693–695.

British Journal of Anaesthesia 1992; **69**: 426–427

BOOK REVIEWS

Atlas of Regional Anaesthesia. By D. L. Brown. Published by W. C. Saunders Co., Philadelphia. Pp. 320; indexed; illustrated. Price £58.00

Although the author no longer works there, this atlas is essentially a product of the Virginia Mason Clinic in Seattle, a major centre for the practice and teaching of regional anaesthesia. Its aim has been to combine in equal proportions words and pictures that describe all the nerve block techniques that may be used in anaesthesia and pain relief, both acute and chronic. It is extremely comprehensive and is the product of one author and one illustrator (Jo Ann Clifford). They are to be congratulated on the very considerable amount of work that must have been necessary for its production. The book is very well produced on high quality paper, although its size and weight would suggest that it is intended as a work of reference, rather than a practical guide. That is a pity, because it does contain some very useful practical information.

The opening chapter gives a little information on local anaesthetic drugs and the specific equipment used in regional anaesthesia such as needles, catheters and nerve stimulators. However, there is virtually no guidance on the assessment of patients, their perioperative management or the specific management of complications. This is a strictly "how to do it" volume. The text is well written and clearly benefits from having a single author. The section on each block is divided into three parts: perspective, placement and "pearls". Under the heading of perspective, there is some advice on patient selection and choice of drugs for the individual block. Placement considers the anatomy and technique of needle insertion, and it is here that the volume is at its strongest. The emphasis is on the need to develop a three-dimensional view of the anatomy and on the need to identify clearly the appropriate landmarks. The "pearls" are the author's attempt to distil his considerable clinical experience down to some helpful hints for the performance of each technique.

The illustrations are considerable in number and usually very clear. However, they are perhaps a little less successful than the text. A significant number have been reproduced against a pale brown background, which rather obscures the detail and for some reason some nerves are coloured brown and others are coloured yellow. This makes for a little confusion. There are a large number of cross sectional illustrations which greatly help the reader develop the three-dimensional anatomical knowledge that is so necessary. The majority of "clinical" illustrations are in fact drawings rather than photographs. Again, these work less well than the anatomical drawings and the few clinical photographs that are in the volume are rather poor in quality.

As this reviewer knows only too well, the ideal instructional text on regional anaesthesia has yet to be produced. However, this is a very useful addition to the list of books that are available. Also, it has been produced at an extremely competitive price, given the quality of production and the very large number of coloured illustrations. It merits a place in every departmental library and on the shelf of every practitioner of regional anaesthesia.

J. A. W. Wildsmith

The Ageing Surgical Patient—Anaesthetic, Operative and Medical Management. Edited by D. L. Crosby, G. A. D. Rees and D. G. Seymour. Published by John Wiley & Sons, Chichester. Pp. 457; indexed; illustrated. Price £65.00.

This book covers the anaesthetic, surgical and medical aspects of perioperative care in elderly patients. Although increasing numbers of elderly patients are being operated on, and 90 % of 30-day postoperative deaths occur in those older than 50 yr, the organization of service, teaching and research has yet to be modified accordingly. With the recent separation of the Royal College of Anaesthetists from the Royal College of Surgeons in London, there is also an increased need to retain the close co-operation of surgeons and anaesthetists so essential for patient welfare. This book focuses on these twin goals.

Nine chapters have been contributed by anaesthetists and surgeons working together, but the format of the chapters is not uniform and the content devoted to anaesthetics ranges from 20 to 30%. Abdominal, urological, vascular, cardiothoracic, gynaecological, neurosurgical, ophthalmic, otolaryngological and orthopaedic surgery are presented, but only the surgical aspects of breast cancer feature. Neither surgery nor anaesthesia can be said to be comprehensively covered.

The three editors' 90 pages of introduction and general principles have somewhat restricted the other contributors in an effort to minimize repetition. The chapters are also variable in the amount of detail provided, as dictated by the amount of commitment to geriatric work. Thus excellent results are evident over a period of 13 years as the percentage of open heart surgery in those older than 60 yr has increased from 1 % to 32 % in the Unit's work described.

Also, although the neurosurgical authors, Maurice-Williams and Pegg, state that little has been written on the subject previously, their success is impressive. The ENT and gynaecological teams, on the other hand, with only 11 % and 4.6 % of elderly patients, respectively, seem less conversant with care of the old. The two authors of the chapter on abdominal surgery, Crumplin and Edwards, have worked together closely to improve care of aged patients for a number of years and consequently they provide a stimulating set of conclusions for future developments.

In the chapter dealing with ophthalmic surgery, which has a proportion of aged patients comparable to that in general surgery (50 % plus), it is asserted that "most ophthalmic surgeons administer their own local anaesthetics so detailed discussion of specific techniques is outside the scope of this book." This chapter makes the equally dubious claims that urological opinion is required for prostatism and that a pulse oximeter may be desirable during local anaesthesia! Despite the relatively small amount of geriatric otolaryngology, this chapter also includes a controversial account of induced hypotension. As the state of competence of circulation to vital organs is erratically diminished by ageing and clinically inassessable, I suggest that deliberate hypotension should be indicated only if it is mandatory for the accomplishment of an operation.

The chapter on orthopaedics builds on the vast experience of the Hastings group in gero-orthopaedic organizational matters and provides sound evidence of the need for a holistic approach with all geriatric operations. Intensive care is quite comprehensively presented in a thoughtful chapter built on experience of a subject which is too rarely documented.

Finally, three chapters cover medico-legal and ethical aspects, risks and future prospects and areas for research. The former has a somewhat dry legalistic flavour, but contains valuable nuggets of information. For example "a surgeon who is not experienced in dealing with the elderly would be advised to consult a colleague who is. For example in assessing the ability of an old patient to give pre-operative consent." Also "It would never be lawful to carry out non-therapeutic research on the incompetent."

The chapter on risk includes the following important sentence: "If death is not inevitable, or the operation will make that death possible in a dignified manner without added suffering, then facilities must be made available so as to ensure the best possible outcome." This rationale is surely not specific to ageing patients, but not always applied to them as ardently as it is in the young. The chapter dealing with future trends, together with a suggested code of practice, has been written by Seymour, the geriatrician editor. Whilst he is renowned for his dedication to the field of perioperative geriatrics, I would have welcomed more input from other geriatricians to combat the majority of anaesthetists' and surgeons' limited knowledge of the various aspects of gerontology and geriatrics.

The text is well presented, with a minimum of errors and a very satisfactory index, but late proof changes seem to have produced odd variations in spacing and there are few references more recent than 1988. Despite these reservations, I commend the book as highly informative to both surgeon and anaesthetist. It should be available in every medical library where it will, no doubt, be indexed under the general surgical section, but I hope it will be cross-referenced for anaesthesia. Anaesthetists have texts more clearly directed to their needs, but they will find this book valuable, if only as a source to which to direct surgeons, nurses and the managers with whom they work.

H. T. Davenport

The Obstructed Airway (Ministry of Defence training film). Produced by The Service Sound and Vision Corporation, Chalfont St Peter, Bucks SL9 8TN. Price £59.95.

It is unusual to be asked to review a video recording. It was a novel experience and possibly may represent what may happen in the future—for example if papers are submitted to learned journals on computer discs. This could be of great benefit to both the Editor and the authors of that paper, as intercommunication and subsequent editing may be made easier. This recording deals with airway management. It is clear, concise and accompanied by excellent graphics.

The first section, which dealt with the basics of airway management, was well illustrated. It showed the effect of jaw movements, position of the body and the effects of gravity on the airway. The use of modern aids, including the Guedel and Laryngeal mask airways, was well demonstrated.

The section on tracheal intubation was excellent, with positive emphasis on technique and the time required to accomplish the manoeuvre. Great emphasis was placed also on the confirmation of the correct placement of the tracheal tube, followed by the old adage of "if in doubt, take it out".

The problem of airway obstruction by foreign bodies was rather dramatic, but nevertheless well demonstrated. It encompassed both civilian and theatre scenarios. Finally, the technique of cricothyrotomy was neatly demonstrated—indeed I have not seen it done so smoothly!

My main problem while reviewing this video was trying to decide which group of people would derive the greatest benefit. I do not believe that anaesthetists would gain a great deal, although it might help those starting out on a career. However, the skilful demonstration of a cricothyrotomy technique would certainly not go amiss, even if shown to the most experienced anaesthetist.

It could certainly be used to teach medical students, nursing staff, paramedical and, of course, military personnel. Ironically, the disadvantage may well be the performance of the cricothyrotomy, which had been made to look so easy. It is probably these groups who would obtain the maximum benefit and, indeed, one would not feel uneasy in recommending this recording to their teachers. The personnel who took part in the design of the video, those who volunteered their services, and those who demonstrated the techniques are to be congratulated on their considerable efforts. In all, a most interesting experience for your reviewer and one which he would not mind repeating.

R. S. Vaughan

Adult Respiratory Distress Syndrome. Edited by A. Artigas, F. Lemaire, P. M. Suter and W. M. Zapol. Published (1992) by Churchill Livingstone, Edinburgh, London, Madrid, Melbourne, New York and Tokyo. Pp. 535; indexed; illustrated. Price £90.00.

This multi-author book on the Adult Respiratory Distress Syndrome (ARDS) brings together more than 100 contributors, 75% of whom are based in Europe and the remainder in North America. The book is divided into sections on Clinical Aspects, Morphology, Pathophysiology, Lung Water, Pulmonary Circulation, Pulmonary Function, Mechanical Ventilation, Therapy and Future Trends. It was astonishing to find that no definition of ARDS was given until chapter 47, the last chapter in the book. It was also surprising to read the old chestnut in the third line of the first chapter that there are 150000 cases of ARDS per annum in the U.S.A.—this oft-quoted guess made in 1972 puts the incidence of ARDS 10 times greater than that found in recent surveys—not a reassuring start to an authoritative text.

There was little new material in the section on morphology, although there was a very good chapter by Bachofen and colleagues with beautiful electron micrographs showing extensive destruction of the alveolar epithelium. This was followed by a very competent section on pathophysiology, with eight chapters on various aspects of this important subject. However, despite the fact that there were good reviews by well known workers in the field, all had the patina of age with few, if any, references after the early 1980s. The section on lung water content and capillary circulation was disappointing; in spite of the compelling evidence that alveolar epithelial destruction is the cardinal feature of ARDS, chapter after chapter discusses *microvascular* permeability. There was little or no discussion of corticosteroids, surfactant, nitric oxide, lung repair or active transport across the alveolar capillary barrier. Reflection coefficient was not indexed and was mentioned only superficially. Permeability of the alveolar capillary barrier was also not indexed and there was no mention of studies published in the past 6 years of barrier permeability in ARDS to ^{99m}TcDTPA or labelled albumin.

The remainder of the book included several essays of interest to a few specialized workers who are already familiar with this work. The penultimate and final chapters are likely to be of most interest to clinicians, although the section on future trends was rather dated. The reviewer concluded that the book is out of date and cannot consequently be recommended. A review article on ARDS published in *British Journal of Anaesthesia* 2 years ago provides a more useful contemporary *résumé* of the subject.

J. G. Jones

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL I

PERIPHERAL NERVE DAMAGE AND REGIONAL ANAESTHESIA

Damage to peripheral nerves at or around the time of a surgical operation has been a well recognized hazard for many years. Regional anaesthetic techniques may be implicated in the aetiology of such damage and there have been isolated reports published [1–3], but for several reasons it is difficult to obtain an accurate assessment of the incidence of the problem or if this has changed over time.

Peripheral nerve damage is not as dramatic or potentially catastrophic as the more central neural damage which may be associated with spinal or extradural techniques. Minor degrees of damage are often unreported and may not even be noticed by the patient. Signs of damage may not become apparent for some time, as interference with the microvasculature of any neural structure may result in the subsequent development of a neuropathy, and in normal clinical practice relatively few patients who have received a peripheral nerve block are seen after operation by the anaesthetist at a time when nerve damage is detectable. Several reports [4–8] of large numbers of upper limb blocks suggest that the incidence of serious damage is very small, but most studies concentrate on immediate rather than late complications. Neurological damage may not become apparent for up to 1 week after the procedure [9]..

Damage may be caused by physical, chemical or ischaemic mechanisms acting alone or in combination and these may be related to a regional anaesthetic technique. There is no good clinical evidence that any particular disease or drug therapy predisposes a particular patient to develop nerve damage after regional anaesthesia,' but it is well known that in some diseases, such as diabetes mellitus, there are alterations to the microvasculature of peripheral nerves and this may alter the effects of trauma to the nerve. Particular care should therefore be exercised when dealing with such patients, although it will be recognized that these are the very individuals who may benefit most from regional anaesthesia.

Needle trauma remains an important factor. Trauma may damage neural blood vessels or neural barriers, cause extra- or intraneural haematoma or oedema, and lead to degenerative changes or discontinuity of fibres. Many techniques require the elicitation of paraesthesiae in order to obtain a reasonable success rate, and even if paraesthesiae are not deliberately sought, they may occur [10]. The presence of paraesthesiae may be associated with a greater incidence of damage, and if they are to be elicited, this should be carried out gently and certainly not repeatedly. It is important that the patient understands clearly what is being sought and that good rapport exists between anaesthetist and patient, as otherwise repeated nerve trauma may occur. For major nerve and plexus blocks, an immobile needle technique is recommended and, should the needle inadvertently move after the commencement of the injection of local anaesthetic, there should not be any attempt to elicit further paraesthesiae.

It has become fashionable to sedate the patient or even administer general anaesthesia before performing a regional block, and to use a peripheral nerve stimulator to identify the correct position of the needle tip. This may be less variable between patients and give rise to less nerve trauma; however, intraneural injection will not be apparent. Intraneural injection is normally painful and should be readily distinguishable from pain caused by distension of a sheath—so-called pressure paraesthesiae. It may cause intraneural compression and ischaemia for 10–15 min [11], with resultant neuropathy. Recently, a patient undergoing surgery to the hand received a general anaesthetic after which median and ulnar nerve blocks at the wrist were performed [Medical and Dental Defence Union of Scotland, personal communication]. After operation, he developed weakness and persisting paraesthesiae in the distribution of the median nerve which was not helped by a carpal tunnel decompression. In the absence of other evidence, it would be hard to refute the suggestion that damage was caused by the intraneural injection and that any signs of this would have been masked by the general anaesthetic.

The needle itself [12], in particular the length of the bevel and its direction are also relevant, as described in a paper in this issue of the Journal [13]. Long bevel needles are certainly less unpleasant for the patient, particularly if injection is being made above the clavicle or at the elbow or wrist, but the use of a short bevel needle may help identify tissue planes, especially for the axillary approach to the brachial plexus. Short bevel needles produce more damage than long bevel needles when they impale nerves, but they are less likely to impale a nerve.

Local anaesthetic agents in clinically used concentrations are not neurotoxic when applied extraneurally. Concern was expressed some years ago about 2-chloroprocaine, when permanent neural damage followed accidental intrathecal injection [14]. This has been ascribed to the combination of the acidity of the solution and the presence of the antioxidant sodium metabisulphite [15]. There may be important differences in the neurotoxicity of substances if these are injected intraneurally and this has been demonstrated with adrenaline [16]. Theoretically, any preservative in the solution might be neurotoxic and it would therefore be wise to use preservative-free solutions for nerve or plexus blocks, as extraneural injection cannot be guaranteed. Accidental injection of the wrong solution is a potential problem which does not appear to have been reported with peripheral nerve block, but has occurred in obstetric practice when potassium chloride was administered extradurally, with devastating consequences. The introduction of chemical agents used in skin preparation is a theoretical rather than a practical problem and the introduction of infection after the injection of local anaesthetic solutions is very rare and has not been implicated in peripheral nerve damage.

Factors unrelated to the anaesthetic may also be responsible [17]. Tourniquets can cause damage to nerves, especially if applied incorrectly or for very prolonged periods of time. Incorrect positioning of the patient is also well recognized as a cause and this can occur with regional and with general anaesthetic techniques. Cases have been reported, after general anaesthesia, in which it has not been possible to identify the causative factor despite extensive investigation; these may represent a lack of observation, rather than indicate the presence of other mechanisms [18].

There are immense practical difficulties involved in conducting a major clinical study of the effect of needle type and other factors which may be involved in the aetiology of nerve damage caused during regional anaesthesia. In the meantime, it would appear wise to concentrate on the use of a meticulous technique. A thorough knowledge of local anatomy is essential before any block is attempted. It may be reasonable to carry out blocks on the lower limb with the patient anaesthetized, as the consequences of minor degrees of neural damage are less severe and it is common to require a combined local and general technique for surgery. This method can certainly not be recommended for trainees working unsupervised who wish to gain more experience of a technique with which they are unfamiliar; this should not be embarked upon lightly for upper limb blocks. More than 40 years ago, Wooley and Vandam [4] stated that it may be prudent to avoid the use of brachial plexus nerve block in persons whose fingers and hands are exceedingly important for the performance of fine work—for example musicians and certain technicians. This advice is still as pertinent today and should be followed unless there are good reasons to the contrary.

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British Journal of Anaesthesia 1992; **69**: 431–432

EDITORIAL II

THE NATIONAL CONFIDENTIAL ENQUIRY INTO PERIOPERATIVE DEATHS 1990

It has long been a cornerstone of anaesthetic practice in the United Kingdom that our actions should be held up to our peers for periodic review. The most immediate examples of this are the regular Mortality and Morbidity meetings held by every Department of Anaesthesia; the existence of such meetings is a requirement for accreditation by the Royal College of Anaesthetists. However, such meetings can yield only a limited number of lessons, bounded as they are by a small initial population of patients, anaesthetics and anaesthetists. The Association of Anaesthetists of Great Britain and Ireland commissioned three reports to address this problem. The first of these to provide a wider information base was the report of 1000 deaths associated with anaesthesia published in 1956 and was derived from voluntary reporting [1]. This was followed by an additional 600 cases 8 years later [2]. These were an important start, but the denominator from which these cases were drawn was unknown. In 1982, Lunn and Mushin presented a prospective review of mortality occurring in the first 6 days after anaesthesia [3]. The introduction to that review acknowledged the need for a co-operative study involving both anaesthetists and surgeons, arguing that the practices of the two specialties were closely linked. That such studies were possible was demonstrated by the work of Beecher and Todd [4] and the triennial *Reports on Confidential Enquiries into Maternal Deaths* which have taken place since 1952 [5]. After much work, the initial Confidential Enquiry into Perioperative Deaths (CEPOD) reported in 1987 [6]. This concentrated predominantly on three London Health Authorities, and several deficiencies in the delivery of care were noted. The study was expanded to encompass a sample of all deaths occurring in association with paediatric surgical or anaesthetic procedures in England and Wales in 1989 as the National Confidential Enquiry into Perioperative Deaths (NCEPOD) [7].

The NCEPOD steering group has now produced its second report (published in May 1992) relating to the period January 1 to December 31, 1990 and examining perioperative mortality in adults [8]. A total of 18817 deaths within 30 days of surgery or anaesthesia were reported to NCEPOD. A sample of 3485 of these was chosen for further review. Questionnaires were sent to the appropriate Consultant surgeon, including an anaesthetic questionnaire to be passed on to the appropriate anaesthetist; 73.6% of the surgical and 65.8% of the anaesthetic questionnaires were returned by the closure date. The difference between the groups was believed to reflect the chosen mode of distribution of the questionnaires. For 90 of these deaths, the patient records could not be obtained for review, at least one being known to have been partly destroyed.

Many of the deaths reported occurred in patients who were elderly (31.5% were older than 80 yr), severely ill (45% were ASA IV or V), or both. For 61.5% of these patients, anaesthesia was administered in the presence of a Consultant or Senior Registrar, and in many of the remainder, discussion with a consultant occurred before or during the procedure. An attempt was made to examine normal practice for the doctors involved in the study group. The first patient on a list chosen at random was also selected for examination as an index case. It is immediately obvious that this population differs markedly from that of the study, being composed largely of young healthy individuals undergoing minor surgery. Although of interest in their own right, the data provided were of limited value for comparison. An additional effort was made to produce a population of survivor patients that nearly matched that of the deaths, but unfortunately this was unsuccessful.

Several general conclusions are drawn in the document. It is noted that there are gaps in the data, caused by a various factors. Notes may be lost, junior staff may move on, notes are incomplete and reports are not returned.

In several cases, the respondents suggested that the absence of suitable facilities (recovery rooms, high dependency units, intensive care facilities) contributed to some of the deaths. The absence of non-medical assistance, or inappropriately trained assistance, for some of these cases is disturbing. These deficiencies can, and should, be corrected.

Delay in operating, particularly in surgery for fracture of the neck of the femur, was implicated as contributing to some of the deaths; the major component of this appeared to be lack of emergency operating facilities. The provision of daytime emergency theatres is suggested, but it is unclear if the surgical expertise is likely to be available during this period, and split-site commitments are likely to worsen this lack of availability. It is noted and approved that the great majority of decisions were made by Consultants or Senior Registrars, that this group provided most of the anaesthesia for the patients who died and that nearly all patients were assessed by an anaesthetist before surgery.

There was a suggestion that non-consultant, non-training grade anaesthetists seem reluctant to call for senior advice, and it is suggested that this group should be actively integrated into the organization and internal review practice of every anaesthetic department, which seems a laudable goal and may prevent a feeling of isolation that may develop in these practitioners.

Many *locum tenens* practitioners provide a wholly satisfactory service, and indeed many are merely "acting up" within their own department to a level for which they are actively seeking a substantive post. However, several of those providing responses to this Enquiry suggested that they were out of practice in the procedures being used in the patients who died. This group may feel particularly vulnerable, and must be actively encouraged to seek help. Those responsible for their supervision may need to pay special attention to the needs of this group.

The final recommendation is not surprising, in that the authors of the report believe that all grades of medical practitioner should take an active part in continuing medical audit and that as a part of this, the National Confidential Enquiry into Perioperative Deaths should continue.

This report may be criticized, as were its predecessors, on the grounds that what is presented is largely a series of anecdotal reports. It is conceded that the data refer to a small fraction, possibly less than 0.7 %, of the surgical population, and that much emphasis is placed on perceived substandard practice, while the overall high standard of care needs to be acknowledged. The power of the Enquiry will always be diminished as long as fuller data about the population from which they are drawn are unavailable. An unsuccessful attempt to correct this was made in this report. Despite this, Mortality and Morbidity meetings have for many years recognized that many lessons may be learned from a story well presented. This report is the summation of many such stories, and the conclusions drawn add weight to the arguments of those making a case for better facilities for our high risk patients in the face of increasing financial restraints.

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British Journal of Anaesthesia 1992; **69**: 433–438

ORIGINAL ARTICLES

PERIPHERAL NERVE INJURY CAUSED BY INJECTION NEEDLES USED IN REGIONAL ANAESTHESIA: INFLUENCE OF BEVEL CONFIGURATION, STUDIED IN A RAT MODEL

A. S. C. RICE AND S. B. McMAHON

SUMMARY

We have studied the immediate and long term (up to 28 days) effects of short and long bevelled needle impalement of the rat sciatic nerve. Three techniques were used to assess neural trauma and its consequences: stained longitudinal nerve sections were assessed by light microscopy and scored for injury; the extravasation of Evan's Blue dye, after antidromic electrical nerve stimulation, was used as a test of unmyelinated fibre function; the flexion withdrawal times from a noxious stimulus were measured. The results of all three experiments suggested that, should a nerve fascicle become accidentally impaled during regional anaesthesia, the lesions induced by short bevelled needles are more severe, more frequent and take longer to repair than those induced by long bevelled needles. Nerve injury induced by short bevelled needles was associated with persisting signs of injury 28 days after the injury. These results suggest that the current practice of using short bevelled needles to prevent nerve injury complicating regional anaesthesia be reassessed. (Br. J. Anaesth. 1992; **69**: 433–438).

KEY WORDS

Anaesthetic techniques: regional. Complications: nerve injury. Equipment: short and long bevelled needles.

Nerve injury during regional anaesthesia may result from several factors. One agent is direct trauma from the injection needle; bevel design and needle size are probably important factors.

The effects of bevel configuration upon perineural injury were examined by Selander, Dhuner and Lundborg [1], although others [2] have modified needle design, to reduce the risk of intraneural injection. Using a method of assessing fascicular injury by measuring the permeability of the perineurial sheath, Selander's group found that the frequency of lesions was greater when a long, as opposed to short, bevelled (45°) needle was used. All the nerves were prepared within 2 h of injury, so the effects of intraneural ischaemia and fibre de- and regeneration were not observed. Despite the limitations of that study, the recommendation was made "that a 45° bevelled needle less frequently produces fascicular damage and should therefore be recommended for use in clinical anaesthesia" and current practice reflects this [3].

However, although Selander, Dhuner and Lundborg [1] did not measure severity of injury to intrafascicular structures, the observation was made: "when this needle (short bevelled) pierced the fascicle with the bevel parallel to the fibres, it seemed to produce somewhat more damage than the long bevelled needle of the same orientation". In microneurography experiments, when electrodes are inserted into human nerves, the symptoms of nerve damage are not apparent until 48–72 h after the injury [4–6]. Others [7] have highlighted the late onset of symptoms after nerve trauma during regional anaesthesia. The experiments presented here examined the histological, functional and behavioural effects of impalement of the rat sciatic nerve observed either within 30 min of injury, or at 7 or 28 days after injury. Long and short bevelled needles were used.

MATERIALS AND METHODS

Needles

We examined two types of injection needle commonly used in anaesthetic practice: a 23-gauge (o.d. 0.63 mm) injection needle with a long (12°) double bevelled cutting edge (Becton Dickinson Microlance 000800) (LB) and a 22-gauge (o.d. 0.71 mm) short (27°) bevelled needle of the type used in regional anaesthesia (Becton Dickinson Ref: 008384) (SB). Both needles were studied with the bevel inserted parallel and transverse to the direction of the nerve fibres.

Animals

Wistar rats of both sexes, weight 142–380 g, were anaesthetized for all surgical procedures. For the recovery experiments, pentobarbitone 40 g kg^{-1} i.p. was used and aseptic procedures followed. After surgery, the wound was closed in layers and recovery was uneventful in all cases. For terminal experiments urethane 1.0–1.25 g kg^{-1} i.p. was used as the anaesthetic agent and a lethal dose was administered at the end of the experiment.

The sciatic nerve was exposed bilaterally from the

This article is accompanied by Editorial I.

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dorsal aspect and the needle introduced into the nerve at mid thigh level at an angle of 45° and left undisturbed for 10 min. The insertion site was marked by light application of carbon suspension on the surface of the nerve [8].

Histology

The animals were killed and a length of sciatic nerve was excised, with an adequate clearance each side of the injury site, either immediately after nerve injury or on the 7th or 28th day after operation. The excised nerves were stored under 4% formal saline. They were then embedded and frozen and longitudinal sections of 50 μm thickness were cut. These were passed through serial alcohols and xylene to remove lipids, then stained in neutral red for 12 min and subsequently dehydrated in serial alcohols and xylene. The sections were examined by light microscopy. All sections were assessed by the same observer who was unaware of which type of needle had been inserted into the nerve.

The sections were examined individually for signs of nerve injury, using three different criteria:

Intraneural disruption. This was defined as the degree of disruption to the internal elements of the nerve and included such factors as the reaction at the site of injury, the gliosis. It was scored on a 0–5 scale, 0 representing no intraneural disruption and 5 representing complete loss of identifiable intraneural elements at the site of injury.

Evidence of axonal degeneration distal to the insertion site. This was observed only in sections taken at either 7 or 28 days. It was scored on a present or absent basis (yes/no). This type of lesion implies axonal injury, without necessarily indicating a lesion of severity sufficient to destroy the supporting structure of the nerve.

Evidence of disorganized regeneration of fibres. This was also observed only in sections taken at either 7 or 28 days after injury and was scored also on a present or absent basis. This pattern of nerve fibre regeneration implies that, not only had axonal damage occurred, but the lesion was of a severity sufficient to damage the supporting structure of the nerve. This pattern of regeneration may result in neuroma formation. Indeed, in nerves displaying these features, gross neuromas-in-continuity were often observed during dissection.

Any experiment which relies upon observation of histological preparations has an inherent degree of subjectivity on the part of the observer, therefore we were unwilling to place undue emphasis on any one histologically observable feature of nerve fibre damage. Consequently, we constructed a global assessment of nerve fascicle injury (which had sufficient security to enable statistical analysis to be performed), in the form of summed nerve injury scores. The data from the intraneural disruption, axonal degeneration and disorganized regeneration observations, in addition to observations of epineural disruption (scored in the same manner as intraneural disruption), were used to calculate the summed nerve injury score. For each needle and bevel configuration at each time point (immediately after injury and at 7 or 28 days), a table of high and low score point allocation was constructed. When each nerve was assessed by the blinded observer, one point was allocated to the low score table if the epineural or intraneural disruption score was less than 2.5 or when no evidence of axonal degeneration or disorganized fibre regeneration was observed. The converse applied to point allocation to the high score group.

Comparison was made using the chi-square test with the Yates' correction.

Extravasation test

This test assessed the functional integrity of the unmyelinated afferent nociceptive fibres, which are generally of a size beyond the resolution of light microscopic techniques. When these neurones are activated by peripheral stimulation or by antidromic nerve stimulation, they release agents which cause vasodilatation and oedema in the peripheral tissues, as observed in the triple response of Lewis. It is possible to quantify the degree of neurogenic oedema produced by measuring the extravasation of the dye Evans's Blue, as described fully elsewhere [9, 10].

Needle penetration (once only, per animal) was performed at the sciatico–sural junction. When positioned, the needle was left *in situ* for 10 min, undisturbed, before withdrawal. All animals underwent sham exposure of the contralateral sciatic nerve, as a control.

Immediately, 7 or 28 days later, both sciatic nerves were exposed from the dorsal aspect. The sciatic nerve was crushed proximally, as were all its distal branches, with the exception of the sural nerve. Both test and control sciatic nerves were mounted on bipolar silver hook electrodes, proximal to the site of impalement. Five minutes after an i.a. infusion of Evan's Blue dye 50 mg kg^{-1}, the nerve was stimulated electrically. Square wave impulses of 5 MA amplitude and 500 μs duration were delivered at a frequency of 2 Hz for 10 min. The impulses in the unmyelinated afferents were conducted peripherally, where they caused agents to be released which resulted in oedema and extravasation of Evan's Blue. Division of C fibres obtunds this effect. The amount of extravasated Evan's Blue in the skin innervated by the sural nerve was measured. Five minutes after stimulation was complete, the animals were killed and transcardially perfused with 0.9% saline 100 ml. This perfusion ensured that the Evan's Blue was flushed from the intravascular compartment, but did not remove the extravasated dye. The sural-innervated skin was dissected bilaterally, weighed and stored in 4 ml of a filtered 70:30 extraction mixture of acetone and sodium sulphide 0.5 g $litre^{-1}$ [9, 10]. The concentration of Evan's Blue dye extracted into the solution was measured by spectrophotometry at a wavelength of 620 nm in glass cuvettes [11] and the concentration of dye in sural skin calculated. Baseline values were obtained from eight animals which had no surgery performed on either limb. Results were expressed as ratios of Evan's Blue concentrations in test to control limbs for each animal and compared with baseline ratios using Student's *t* test for unpaired data.

TABLE I. *Histological features of nerve injury caused by long (LB) and short (SB) bevelled needles aligned both parallel (p) and transverse (t) to the direction of nerve fibres. Mean (SEM) intraneural disruption scores immediately after (day 1) and at 7 and 28 days after injury (scored on a scale of 0–5 (see methods)); percentage of nerves which were observed to display features of axonal degeneration at 7 and 28 days after injury; percentage of nerves which were observed to display features of disorganized regeneration at 7 and 28 days after injury*

	Intraneural disruption score	Axonal degeneration (%)	Disorganized regeneration (%)
Day 1			
LB(p)	1 (0.58)	—	—
LB(t)	4 (0.3)	—	—
SB(p)	2.5 (0.42)	—	—
SB(t)	3.75 (0.72)	—	—
Day 7			
LB(p)	1.25 (0.43)	0	50
LB(t)	3.5 (0.37)	50	100
SB(p)	4 (0.25)	100	100
SB(t)	4.25 (0.28)	75	100
Day 28			
LB(p)	0.67 (0.16)	0	0
LB(t)	1.33 (0.16)	100	0
SB(p)	4.25 (0.14)	100	100
SB(t)	3.25 (0.49)	75	75

Limb withdrawal test

The hind limb flexion reflex withdrawal time after foot immersion in water at 49 °C was measured, in order to assess the integrity of both the afferent and efferent limbs of the reflex arc associated with the response to a noxious stimulus and its spinal processing. The left sciatic nerve was used as the test side and the right sciatic nerve was exposed in a sham operation, as a control.

Under anaesthesia, a single needle was inserted into the left sciatic nerve, just proximal to the sciatico-sural junction. The needle was left *in situ*, undisturbed, for 10 min, then withdrawn and the wound closed.

The animals were examined before and at 1, 3, 7, 14, 21 and 28 days after needle insertion. They were observed initially for the presence of any gross motor deficits and behaviourial abnormalities as they moved around their cages. They were inspected for evidence of autotomy, as described by Wall, Scadding and Tomkiewicz [12].

The lateral border of the foot was immersed in hot water (49 °C) and the time for the animal to actively withdraw the limb was measured. The test and control sides were tested alternately. The first readings from each side were ignored and then three subsequent readings for each side were taken; from these values, test and control side means were calculated. The withdrawal times were expressed as a difference between the test and control means. Therefore, a positive score may be taken to represent hypoalgesia of the test side (i.e. a test time of longer duration than observed with the control). Conversely, a negative score may be taken to represent hyperalgesia of the test side. Statistical comparison with baseline values was made using Student's *t* test for paired data.

RESULTS

Histology

Fifty-six animals were studied; 19 were killed immediately after injury, 19 at 7 days and 18 on the 28th day after operation. The limitations of placing excessive emphasis upon one histological feature of nerve fibre injury were outlined in the methods section. However, such data are shown here so that the trends may be observed, before examining the global assessment of nerve fibre injury, which was subjected to statistical analysis.

Table I shows the mean scores for intraneural disruption and the frequency of axonal degeneration and disorganized regeneration. The LB needles, when the bevel was aligned in a parallel fashion, appeared to induce less intraneural damage than the SB needles of either orientation or the LB transverse needle, both immediately after injury and 7 days later. However, by 28 days the injuries caused by the LB needle (both orientations) appeared to be resolving, whereas both orientations of the SB needle displayed evidence of continuing processes. When the frequency of distal axonal degeneration was examined, this feature was observed only in sections taken from animals killed at 7 and 28 days after surgery. This pattern of injury was not observed in nerves impaled by the LB needle when its bevel was aligned parallel to the nerve fibres. Axonal degeneration was apparent in nerves impaled by all other types of needle insertion and there appeared to be no clear difference between the SB and the LB transverse needles. With regard to the frequency of disorganized and random regrowth of axons, as this is a regenerative process it was also observed only in the sections taken at 7 and 28 days after impalement. Although this feature was apparent 7 days after all types of needle injury, the LB parallel needle appeared to induce such changes with the least frequency. By 28 days neither orientation of the LB needles induced these changes. In contrast, most nerves impaled by the SB needles exhibited such changes both at 7 and 28 days.

The summed nerve injury scores are displayed in figure 1. Statistical comparison was made using the chi-square test with Yates' correction. The trend observed in the above data was that the LB parallel needle appeared to induce the least severe nerve

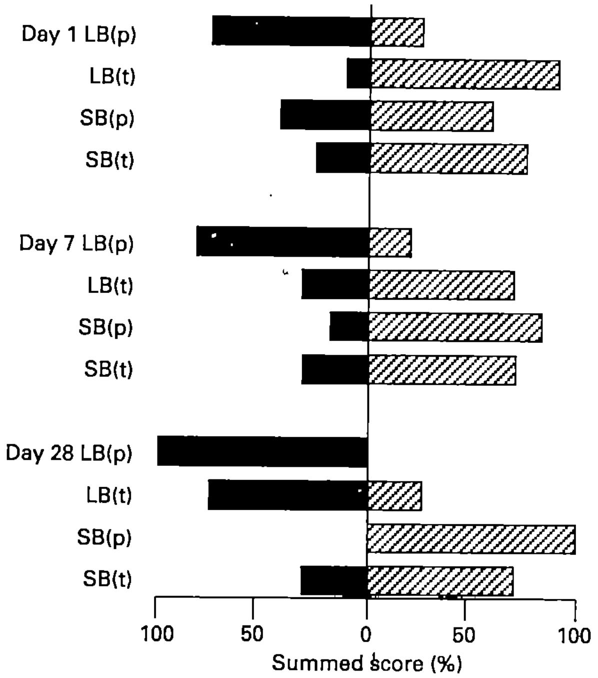

FIG. 1. Summed nerve injury scores obtained from rat sciatic nerves examined immediately after (day 1) and at 7 and 28 days after nerve impalement by long and short bevelled injection needles aligned parallel (p) or transverse (t) to the direction of nerve fibres. The x axis represents the percentage of summed nerve injury scores for each type of needle and each time point. The percentage of high scores (▨) (see methods for greater detail) are shown to the right of the midline and the percentage of low scores (■) to the left.

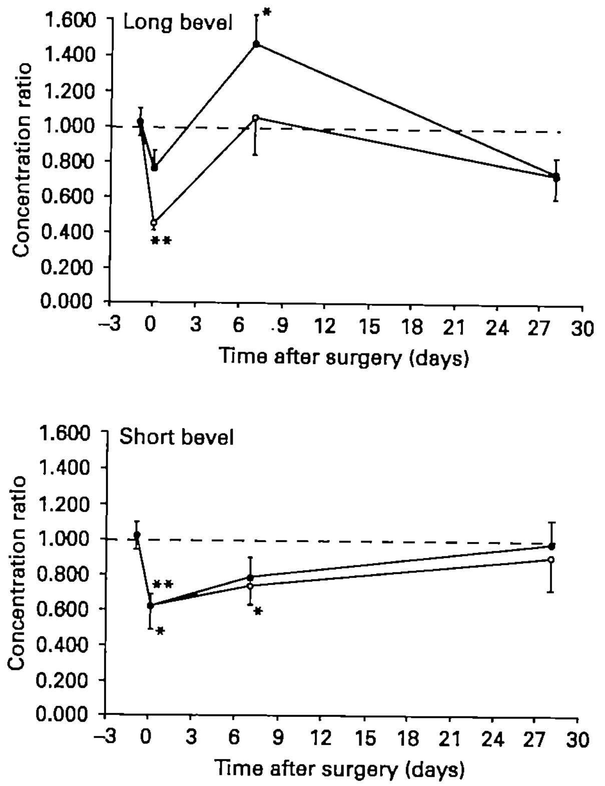

FIG. 2. Concentration of Evan's Blue dye extravasated into the skin innervated by the sural nerve after electrical antidromic stimulation of afferent C fibres. The results are expressed as the mean (SEM) ratio of the concentrations in test and control limbs, plotted against time (days following impalement with injection needles). ● = Transverse orientation of needle; ○ = parallel orientation. $^*P < 0.05$; $^{**}P < 0.01$ between groups (unpaired t test).

injury, therefore comparisons were made with the summed nerve injury data from this needle.

Immediately after nerve injury there was little difference between the summed nerve injury scores, although transverse orientation of the LB needle was associated with greater scores than when the same needle was introduced in a parallel manner (LB parallel *vs* LB transverse: $P < 0.05$; LB parallel *vs* SB parallel: $P < 0.5$; LB parallel *vs* SB transverse: $P < 0.5$). However, at 7 days after injury, the LB parallel needle achieved significantly smaller summed nerve injury scores compared with the other needles (*vs* LB transverse: $P < 0.05$; *vs* SB parallel: $P < 0.01$; *vs* SB transverse: $P < 0.05$). By 28 days there was no significant difference between the LB needle summed nerve injury scores, which were significantly less than SB needles scores (*vs* LB transverse: $P < 0.5$; *vs* SB parallel: $P < 0.01$; *vs* SB transverse: $P < 0.01$). Signs of injury after nerve impalement with the SB needle persisted for longer than after the LB needle-induced injury. When bevel orientation was ignored and the summed scores were combined for each type of needle, there was no significant difference ($P > 0.5$) between LB and SB needles immediately after nerve impalement, but the LB needles were associated with significantly smaller scores at 7 ($P < 0.01$) and 28 days ($P < 0.01$).

In summary the LB needle, when introduced with the bevel aligned parallel to the direction of passage of nerve fibres, generally induced injury less frequently and such lesions were less severe and more rapidly repaired injury than lesions caused by the other needles. There was persistence of the structural changes after SB needle-induced nerve injury 28 days after nerve impalement.

Extravasation

Results from 63 animals were included in the analysis. Eight animals were in the control (baseline) group, 20 animals were killed immediately after injury and 17 and 18 on the 7th and 28th days after operation, respectively.

The data were analysed by comparing the concentration of Evan's Blue in the sural skin of the operated limb (test) with that in the contralateral sham operated limb (control) and the result expressed as a ratio (fig. 2). Both orientations of the SB needle and the parallel orientation of the LB needle caused a significant decrease in extravasation of Evan's Blue immediately after nerve injury. There was no significant change with the LB transverse needle. At 7 days after injury, the LB parallel and SB transverse groups showed no significant change from baseline readings, but the SB parallel and LB transverse differed significantly from baseline values. In the case of the LB transverse needle, there was a period of increased extravasation at 7 days. It is not clear why this increase occurred, but it could possibly reflect overproduction of neuropeptides, which mediate this action, as part of the repair process. The results of the flexion withdrawal test also showed

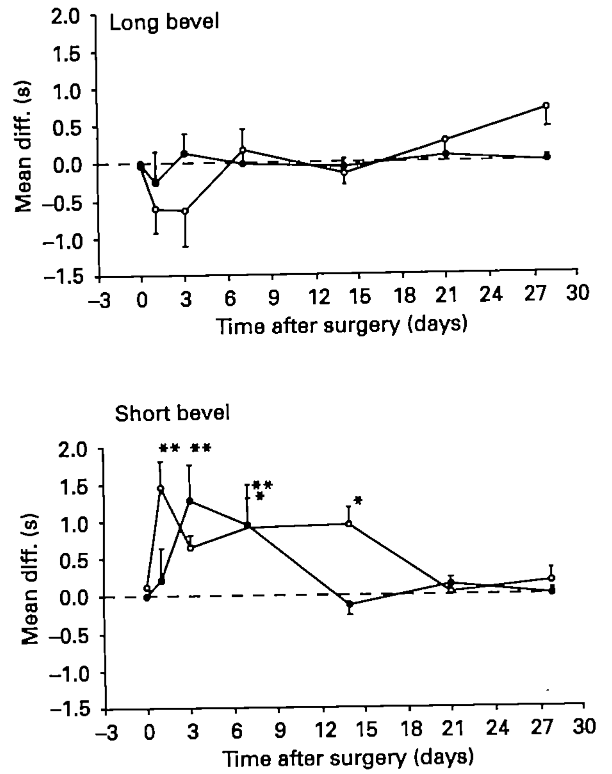

FIG. 3 Mean (SEM) differences between test and control limb flexion withdrawal times up to 28 days after nerve impalement by injection needles. ● = Transverse orientation of needles; ○ = parallel orientation. $*P < 0.05$; $**P < 0.01$ between groups (paired *t* test).

differential effects. By 28 days none of the needles was associated with a significant change in Evan's Blue extravasation from baseline values, indicating a return of nociceptive neurone function to normal.

Behavioural tests

Results from 40 animals were included in this section, of which 20 were killed after the measurement taken on the 7th day after operation. There was no evidence of autotomy, motor defects or abnormal behaviour in any animal at any time.

The results of the foot withdrawal test are shown in figure 3. There were no significant changes in the flexion withdrawal response at any time after the LB needle was used. In contrast, both orientations of the short bevelled needles produced significant differences in response lasting up to about 2 weeks, but these had also returned to normal by 28 days. The direction of the changes observed with the SB needle suggest that the skin innervated by the impaled nerve became hyposensitive. The changes with the SB needle were therefore significantly more severe and resolved after a longer period than did injuries resulting from nerve impalement by the LB needle.

DISCUSSION

The results of these experiments suggest that when nerve fascicles are impaled by commercially available injection needles (of similar diameter), lesions occur less frequently, are less severe and are repaired more rapidly if they are induced by an LB needle compared with an SB needle. The least traumatic bevel orientation occurred when an LB needle was introduced with its bevel parallel to the course of the nerve fibres. Persistence of signs of injury were apparent 1 month after SB needle impalement and such lesions tended to regenerate in a disorganized fashion.

The results of this study would appear to disagree with the other study [1] which has examined this subject. However, there is a fundamental difference between the two studies, which should be noted when a comparison is made: Selander, Dhuner and Lundborg [1] examined the frequency of injury to the perineural membrane, which surrounds nerve fascicles, after nerve trunk impalement. We have examined the frequency, severity and consequences of injury to fascicular contents after *in vivo* impalement of nerve fascicles.

Selander and his colleagues [1] examined the frequency of lesions in the nerve fascicles of an isolated rabbit sciatic nerve, using 14° and 45° (ground from 14°) bevelled needles inserted both parallel and transverse to the course of nerve fibres. They used a technique of assessing fascicular injury, which estimated the integrity of the perineurium by the transfer of Evan's Blue across this membrane. They also performed a similar experiment with the nerve intact in an *in vivo* model, but the animals were killed only 2 h after nerve injury. Perineural lesions were more frequent with the LB needles but, although severity of injury was not formally assessed, the authors did remark that the SB parallel needle: "seemed to produce somewhat more damage than the LB needle of the same orientation." When the *in vivo* model was examined, there was less fascicular injury with both needles and both bevel orientations, probably because of fascicular sliding, but there was still a greater frequency of perineural injury with LB needles. In the *in vivo* studies, intraneural haemorrhage was observed with both needles, but severity of injury was not discussed.

There are further differences between this and the study by Selander's group [1] which should be considered. Different animal models were used: the rabbit sciatic nerve preparation used in the earlier study is multi-fasciculated and the authors observed sliding of fascicles away from the tip of the needles. They discussed the significance of this and postulated that it may have been a factor in the differing frequency of fascicular injury after the use of SB and LB needles. The rat sciatic nerve used in our study consists of only one fascicle at mid-thigh level and nerve (fascicle) penetration was ensured in all cases. Although there was a direct comparison between the two needle types, there was no control group in Selander's study, to validate the sensitivity of the experimental methods and the effects of surgery; 50 % of the preparations were *in vitro* isolated nerves so that the effects of ischaemia, haematomata etc. were not apparent. In the *in vivo* part of the same study, intraneural haematomata were certainly observed and the results of this section of the study may also have been confused by the use of an intraneural injection of 0.05 ml of Evan's Blue. It has been shown subsequently that the intraneural injection of volumes as small as 100–50 µl may generate intraneural pressures which may exceed capillary perfusion pressure for as long as 10 min and thus cause neural ischaemia [13]. The results were confused further by intrafascicular injection of dye in six cases.

In human microneurography, the symptoms of nerve injury do not generally develop immediately after the injury, but may have their onset several days later [4, 5]. Supporting evidence is given in animal studies [6, 8]. Löfström [7] also observed that there was a delay in the onset of symptoms after accidental nerve injury during regional anaesthesia. For these reasons, we examined the effects of nerve injury for 28 days after impalement. Selander, Dhuner and Lundborg did not extend their study into this period [1].

Selander's study may also have been complicated by the fact that, for the *in vitro* study [1], needles of differing diameters were used and the reader is not informed in which bevel group the larger needles were used. Another study has demonstrated the effect of needle size on the frequency and severity of nerve injury [6]. The present study used a consistent and similar size of needle (commercially available) in each group.

Whilst this study demonstrates some advantages of using LB needles in respect of nerve injury, it has not examined the fact that sharper and therefore longer bevelled needles are more comfortable for the patient [14]. This fact was appreciated by the pioneers of regional anaesthesia [15].

In conclusion, this study provides evidence from several different experiments which show that, should accidental nerve fascicle penetration occur, then the frequency, severity and time course of intrafascicular injury would be greater when SB, as opposed to LB, needles were used. Therefore, we cannot confirm the suggestion of Selander, Dhuner and Lundborg [1] that "a 45° bevelled needle less frequently produces fascicular damage and should therefore be recommended for use in clinical anaesthesia". Indeed, the results of our study suggest that there may be grounds for recommending the use of LB needles, especially if the bevel is aligned parallel to the nerve fibres.

The ability of various types of bevel configuration to impale human nerves and their fascicles in the clinical (percutaneous, as opposed to the *in vitro* or surgically exposed) setting, remains to be ascertained. We were unable to locate any reported human study which demonstrates a lesser incidence of nerve injury symptoms after regional anaesthesia performed with SB compared with LB needles, whether or not paraesthesiae were elicited. Therefore, clinical studies should be performed before any definite recommendations can be made regarding the use of differently configured needles in regional anaesthesia. However, the longer regenerative period and high incidence of disorganized fibre regeneration after injury with SB needles must give particular cause for concern. The optimum bevel configuration of needles used in human regional anaesthesia remains to be ascertained.

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[redacted]

TABLE I. *Physical characteristics of the patients in the three groups (mean (range or* SD*))*

	Isoflurane	Halothane	Midazolam
Number	15	16	10
Age (yr)	37.0 (19.7–65.1)	37.8 (21.6–54.7)	37.3 (15.3–57.2)
Weight (kg)	63.7 (11.2)	68.2 (7.6)	66.8 (14.2)
Sex (M:F)	8:7	8:8	4:6

TABLE II. *Pharmacokinetic variables for each group (mean (*SD*)).* Vd^{ss} = *Volume of distribution at steady state;* $T_{\frac{1}{2}}^{\beta}$ = *elimination half-time.* ** *Significant difference amongst the three groups (P < 0.01, Kruskal–Wallis test)*

	Isoflurane	Halothane	Midazolam
V_1 (litre)	4.48 (0.65)	4.00 (0.76)	3.94 (0.69)
Vd^{ss} (litre)	8.71 (0.70)	8.00 (1.02)	7.97 (1.26)
Clearance (ml min^{-1})**	424 (54)	362 (44)	372 (37)
$T_{\frac{1}{2}}^{\beta}$ (min)	18.7 (2.8)	20.0 (3.0)	19.4 (3.2)

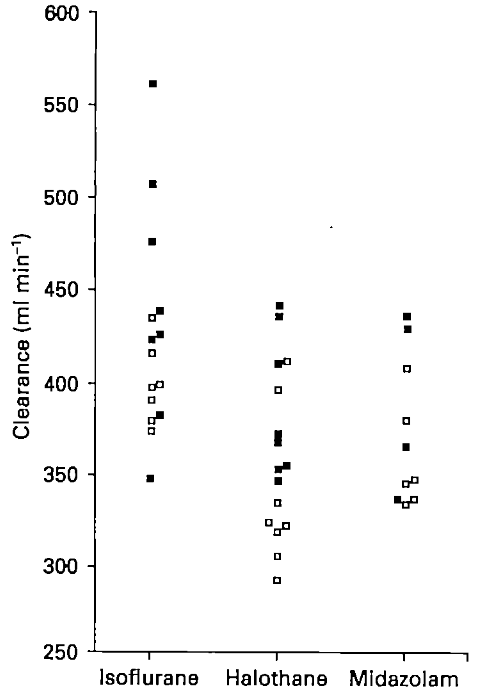

FIG. 1. Values of atracurium clearance for each patient according to the anaesthetic technique and sex (■ = male; □ = female).

samples; the other, in a vein in the opposite forearm, was used for administration of atracurium.

After 20 min, when the end-tidal concentration of volatile anaesthetic agent (if used) was stabilized, atracurium 0.25 mg kg^{-1} was given by constant rate infusion over a period of 10 min. Ventilation was controlled and the trachea intubated when appropriate; end-tidal carbon dioxide tension was maintained in the range 4.0–5.3 kPa (Datex Capnomac). Pharmacological antagonism of neuromuscular block was not used.

Blood samples (2.5 ml) were obtained before and at 1, 2, 4, 6, 8 and 10 min after the start of the infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75 and 90 min after the end of the infusion. The heparinized blood samples were immediately acidified and cooled, and plasma was separated promptly. The plasma was frozen rapidly in liquid nitrogen and stored at −20 °C until subsequent analysis. Details of the analysis of plasma concentration of atracurium have been given previously [7].

Data analysis

Equations arising from a two-compartment pharmacokinetic model with elimination from both compartments were fitted to the plasma concentration profile, using non-linear least squares regression as described previously [7]. This allows the identification of the central volume of distribution, V_1, and the hybrid elimination rate constant, β, and hence the elimination half-time. The clearance and steady state volume of distribution were estimated using standard non-compartmental formulae [9]. Volume terms were expressed as absolute values, and not divided by body weight [10].

Comparisons between the groups and between the sexes were performed using the Kruskal–Wallis and Mann–Whitney rank sum tests, respectively. The relationship between pharmacokinetic variables and age was examined using Pearson's correlation coefficient. Where a pharmacokinetic variable appeared to be affected by more than one explanatory factor, multivariate linear regression was applied; the significance of added regressors was tested using the F test.

RESULTS

Estimates of the pharmacokinetic variables are summarized for each group in table II as mean (SD).

Effect of anaesthetic technique

The clearance was greater in the group anaesthetized with isoflurane than in the two other groups (Kruskal–Wallis $H = 10.4$, $P < 0.01$). This is illustrated in figure 1, in which the values of clearance are shown for each patient by anaesthetic technique and sex.

Both the central and steady state volumes of distribution were also greater in the group anaesthetized with isoflurane, but these differences were not significant (central volume of distribution: Kruskal–Wallis $H = 4.52$, $P > 0.1$; steady state volume of distribution: $H = 5.84$, $P > 0.05$). Although the elimination half-time was shortest in the group anaesthetized with isoflurane, and longest in the group anaesthetized with halothane, the differences between the groups are small and not significant.

Effect of age

The univariate correlation of each of the pharmacokinetic variables with age when all the patients are considered together is shown in table III. There is a

TABLE III. *Univariate correlation of each pharmacokinetic variable with age when the patients from all three groups are considered together (r = Pearson product moment correlation coefficient; n = number of subjects). P = significance of the correlation, evaluated by the t test of the hypothesis that there is no correlation. Abbreviations as in table II*

	r	n	P
V_1 (litre)	−0.173	41	> 0.1
Vd^{ss} (litre)	0.121	41	> 0.1
Clearance (ml min^{-1})	−0.345	41	< 0.05
$T_{\frac{1}{2}}^{\beta}$ (min)	0.582	41	< 0.001

significant negative correlation between clearance and age, and a significant positive correlation between elimination half-time and age (fig. 2). The two measures of volume of distribution were not significantly correlated with age.

Effect of sex

The possible difference in volume of distribution between the sexes was evaluated using the Mann–Whitney rank sum test, considering the patients from all the three groups together. There was no significant difference between the sexes in either the central volume of distribution (Mann–Whitney $U = 162$; $P > 0.1$) or the steady state volume of distribution (Mann–Whitney $U = 170$; $P > 0.1$).

In view of the relationships demonstrated above between elimination half-time and age, and between clearance and both age and anaesthetic technique, further analysis was undertaken using multiple linear regression. The details of the effect of sex on clearance in the context of a regression of clearance on age, sex and two dummy parameters to separate the three groups is shown in table IV (upper panel); clearance was greater in male subjects, by an average of 49 ml min^{-1}.

The influence of sex on elimination half-time in the context of a bivariate regression of half-time on age and sex is shown in table IV (lower panel). There was a significant difference between the sexes, the elimination half-time being greater by a mean of about 1.9 min in females. Addition of two further parameters to the regression (not shown in table IV), to separate the three groups, failed to reduce the residual error significantly.

DISCUSSION

Description of the pharmacokinetics of atracurium is complicated by its unique mechanisms of degradation; it may be expected to undergo spontaneous decomposition at any site in the body. However, the identification of a compartmental pharmacokinetic model with peripheral degradation is not possible

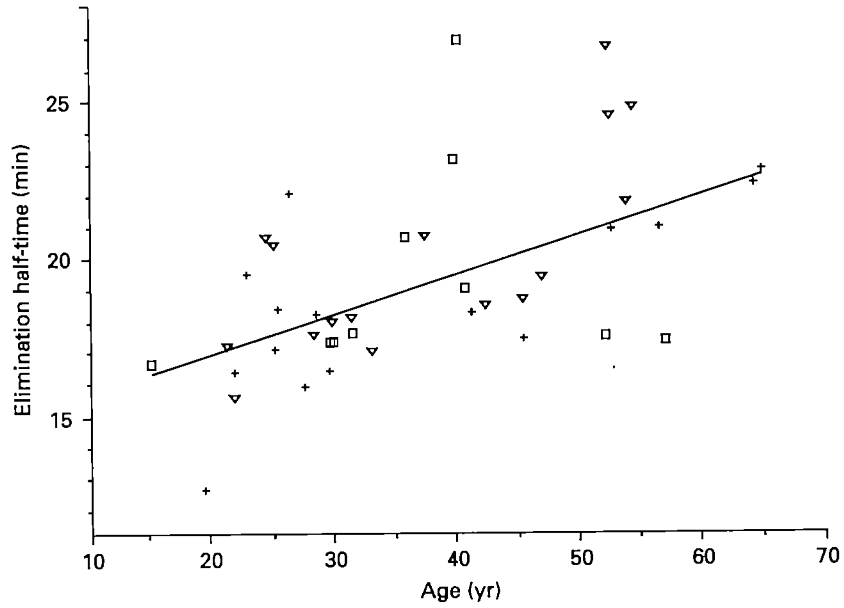

FIG. 2. Values of atracurium elimination half-time plotted against the age of the patient; there is a significant positive correlation ($r = +0.58$; $P < 0.001$). The least squares regression line is shown. + = Isoflurane; ▽ = halothane; □ = midazolam.

TABLE IV. *Relationship between clearance and sex of the patients, in the context of a multivariate linear regression of clearance on age, sex and anaesthetic technique, and relationship of elimination half-time to sex in the context of a bivariate regression on age and sex: regression coefficients and their standard errors, values of* F *and* P *for the inclusion of sex in the final model and degrees of freedom of the numerator and denominator*

	Regression coefficient	SE	F	d.f.	P
Clearance (ml min^{-1})					
Sex (m = 1; f = 0)	49.3	12.0	16.98	1,36	< 0.001
$T_{\frac{1}{2}}^{\beta}$ (min)					
Sex (m = 1; f = 0)	−1.86	0.75	6.26	1,38	< 0.025

[11]; the rate of peripheral degradation cannot be identified from the plasma concentration profile alone. Whilst this does not affect the estimates of central volume of distribution or elimination half-time, the model peripheral volume, and inter-compartmental rate constants cannot be estimated [12]. Furthermore, standard non-compartmental formulae for plasma clearance and steady state volume of distribution (as used here) may not be applied without error, for their derivation depends upon the assumption that all elimination may be considered to occur from the sampled compartment [9]. The standard formula: *Clearance = Dose/AUC* gives a value which overestimates the plasma clearance (defined as the volume of plasma cleared of drug in unit time) by a factor related to the fraction of drug eliminated outside the sampled compartment. Whilst recognizing these difficulties, we have applied here both compartmental and non-compartmental analyses, in an attempt to provide a concise and objective summary of the data. Unlike some workers [6, 13], we did not measure the rate of breakdown of atracurium in the patients' plasma *in vitro* in an attempt to define the rate of "organ independent" clearance.

The present finding that the elimination half-time was increased with advancing age is consistent with both previous reports on the subject [5, 6], although none of the patients in the present study was as old as those studied by either Kitts and others [6] (whose elderly patients were aged 74–76 yr) or by Kent, Parker and Hunter [5] (71–97 yr). When the present results are considered together with those two previous studies, and in the absence of any conflicting evidence, we may have considerable confidence in the conclusion that the elimination half-time of atracurium increases with advancing age.

In the present study, this was related to a reduced clearance in the elderly, in contrast with the two previous studies [5, 6]. The isolated finding of Kitts and others [6] that distribution volume increased in the elderly has not been confirmed. Indeed, the volume of distribution was found to be reduced in the elderly for tubocurarine, dimethyltubocurarine [3] and vecuronium [4], and to be unchanged for pancuronium [1, 2].

It seems difficult to account for the presently reported effects of age in terms of the spontaneous degradation of atracurium, for all the patients were normothermic, without metabolic derangement and were undergoing artificial ventilation to normocapnia. It is tempting to point to a deterioration in function of liver and kidneys with advancing age [14], and in this respect the present finding that clearance is reduced with advancing age lends at least qualitative support to the finding by Fisher and others [13] that about 61% of total atracurium clearance is organ dependent.

There have been no formal studies of the effect of sex or of anaesthetic technique on the pharmacokinetics of the non-depolarizing neuromuscular blocking drugs, and so direct comparison of the present results, on the effect of sex, with previous work is not possible. It is clear, however, that sex exerts an influence on the pharmacokinetics of several drugs [15], and the sexes differ in the activity of plasma esterases [16]. Whilst the role of esterases in the metabolism of atracurium is uncertain, the degradation of atracurium *in vitro* is more rapid in plasma than in buffer at the same pH, and the rate of degradation is slowed by the esterase inhibitors [17]. Thus the present finding of a difference between the sexes in the clearance and half-time of atracurium awaits confirmation and remains unexplained; to suggest a role for ester hydrolysis is speculative.

There is a paucity of information on the effects of anaesthesia on the pharmacokinetics of the non-depolarizing neuromuscular blocking drugs. Plainly, the pharmacokinetics of therapeutic doses of atracurium cannot be studied in the absence of an anaesthetic, and so the elucidation of the effects of anaesthesia must be comparative. In a study similar to this, it was found that halothane (0.5–0.7% or 1.0–1.2% end-tidal) did not affect the pharmacokinetics of tubocurarine compared with a neuroleptanaesthetic technique [18]. Likewise, the clearance of vecuronium was found to be similar in three groups of patients anaesthetized with enflurane, isoflurane or fentanyl [19]. The present finding, that the clearance of atracurium was reduced by halothane and by midazolam supplementation of anaesthesia compared with isoflurane, finds no precedent amongst previous studies of the non-depolarizing neuromuscular blocking drugs.

It is increasingly clear that volatile anaesthetic agents influence the disposition of several drugs including fentanyl [20] and verapamil [21] in the dog, and lignocaine in man [22]. Moreover, different volatile anaesthetic agents may have different effects [23]. Fentanyl and verapamil are more lipophilic than atracurium, and have a different pharmacokinetic profile, yet it is clear that anaesthesia has a profound effect on the disposition of several drugs, and on regional blood flow distribution [24].

Whilst hepatic blood flow is better preserved during anaesthesia with isoflurane than with halothane [24], the clearance of atracurium is considerably less than the hepatic blood flow, and its hepatic extraction must be low. In view of other evidence that atracurium undergoes substantial organ-dependent metabolism [13], it is conceivable that the present finding that clearance is affected by the anaesthetic technique reflects the effect of anaesthetic agents on organ blood flow or function.

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British Journal of Anaesthesia 1992; **69**: 444–446

ETOMIDATE SHORTENS THE ONSET TIME OF NEUROMUSCULAR BLOCK

R. S. GILL AND R. P. F. SCOTT

SUMMARY

We have studied 30 healthy patients allocated randomly to receive thiopentone, propofol or etomidate in equipotent doses followed by vecuronium 0.1 mg kg^{-1}. Haemodynamic variables and time to 100% neuromuscular block were measured. The patients receiving etomidate had a significantly shorter onset time of neuromuscular block compared with those receiving the two other i.v. induction agents. There was a significant negative correlation between onset time of neuromuscular block and the maximum percent change in mean arterial pressure. (Br. J. Anaesth. 1992; **69**: 444–446)

KEY WORDS

Anaesthetics, intravenous: etomidate, propofol, thiopentone. Neuromuscular relaxants: vecuronium. Pharmacodynamics: onset time, neuromuscular block.

The rate of onset of neuromuscular block is determined by the rate at which a pharmacologically effective concentration is achieved in the biophase, in this case the neuromuscular junctional cleft [1]. This is influenced by the dose of drug, its pharmacokinetic profile (volume of distribution, buffering by non-specific binding to mucopolysaccharides and elimination half-life), the rate of association with cholinoceptors, the rate of perfusion of the junctional cleft and drug potency [2].

The rate of equilibration between plasma and junctional cleft concentrations is governed by the dose of neuromuscular blocker, the speed of injection (bolus effect) and by the amount of muscle perfusion. Muscle perfusion may be affected by altered cardiovascular physiology, particularly during the period of induction of anaesthesia.

Enhanced muscle blood flow has been shown to shorten the onset time of neuromuscular block [3], whilst decreased muscle perfusion secondary to hypothermia or low cardiac output delays onset time [4, 5].

Most research into the onset of neuromuscular block for different neuromuscular blockers has been comparative. This paper presents data from a randomized prospective study, designed to test the hypothesis that etomidate, with its favourable haemodynamic characteristics, may be associated with a shorter onset time of neuromuscular block compared with other i.v. induction agents.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Thirty ASA class I or II patients gave informed consent for the study and were allocated randomly to one of three groups, to receive thiopentone 5 mg kg^{-1}, etomidate 0.3 mg kg^{-1} or propofol 2.5 mg kg^{-1}. The patients were aged 18–65 yr, weighed 50–110 kg, and were undergoing elective surgical procedures. We excluded any patient suffering from cardiovascular or neuromuscular disorders, or taking medications which might interfere with normal cardiovascular physiology or neuromuscular transmission.

Premedication consisted of oral temazepam 10–20 mg and metoclopramide 10 mg. Before i.v. induction, baseline mean arterial pressure (MAP) and heart rate (HR) were recorded using a Datascope Accutorr 3Sat non-invasive pressure and pulse oximeter monitor. MAP and HR were used as indirect indicators of muscle perfusion. The different i.v. induction agents were administered into a fast flowing infusion of sodium chloride over 5–10 s. After i.v. induction, the ulnar nerve was stimulated supramaximally using surface electrodes at the wrist, with repetitive train-of-four stimuli. The evoked compound electromyogram of thumb adduction was recorded using a Datex Neuromuscular Transmission Monitor (NTM). After baseline calibration of this device, vecuronium 0.1 mg kg^{-1} was administered over 5 s.

MAP and HR were measured non-invasively and recorded every 1 min until 100% depression of the first twitch of the train-of-four was observed. During this time anaesthesia was maintained with 50% nitrous oxide in oxygen.

TABLE I. *Patient data (mean (range or SEM))*

	Etomidate	Thiopetone	Propofol
Age (yr)	42.8 (25–56)	48.3 (31–64)	41.2 (26–65)
Weight (kg)	74.2 (3.86)	65.3 (3.09)	73 (5.06)

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TABLE II. *Onset time, maximum percent changes in mean arterial pressure (MAP) and heart rate (HR) (mean* (SEM) *[range]). Baseline = actual value of mean baseline MAP or HR.* *$P < 0.05$; ***$P < 0.001$—*ANOVA and linear contrast*

	Etomidate ($n = 10$)	Thiopentone ($n = 10$)	Propofol ($n = 10$)
Mean onset time (s)	144 (16)* [40–220]	197 (21.1) [80–300]	206 (21.2) [80–280]
MAP			
Max. % change	12.1 (6.5)*** [−14 to 44]	−16.3 (2.2) [−5 to −28]	−30.2 (4.6) [−2 to −56]
Baseline (mmHg)	91.2	92.9	98.2
HR			
Max. % change	4.39 (8.9) [−44 to 48]	13.3 (5.13) [−24 to 29]	9.18 (4.9) [−12 to 26]
Baseline (beat min^{-1})	83.4	81.5	79.2

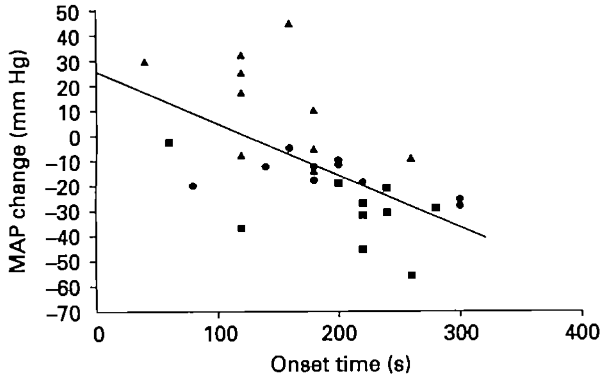

FIG. 1. Correlation between onset time and maximum percent change in MAP in the etomidate (▲), thiopentone (●) and propofol (■) groups. $r = -0.56$; $P < 0.001$.

The results were analysed with the Systat statistical package (Systat Inc, Evanstone Il), using a two-way analysis of variance and linear contrast to calculate the differences between the three groups. Differences were taken to be statistically significant at $P < 0.05$. Results are expressed as mean (SEM).

RESULTS

There were no significant differences between the three groups (table I).

Maximum changes in MAP and HR that occurred between induction and maximal block (100% depression of the first twitch of the train-of-four) were calculated as percentage of baseline value (table II).

Patients in the etomidate group had a significantly shorter onset time than patients in the two other groups ($P < 0.05$). There was a significant difference in the maximum percent change in MAP between all three groups ($P < 0.001$). In addition, there was a significant negative correlation between onset time and the maximum percent change in MAP (fig. 1) ($r = -0.56$, $P < 0.001$).

DISCUSSION

Onset time of neuromuscular block may be influenced by several factors. Standardization of anaesthetic technique is important before any effective comparison is made. In particular, the starting point and end-point in the measurement of onset time, the mode of neuromuscular monitoring and the anaesthetic agents used should be clearly defined. Previous research has shown significantly shorter onset times during nitrous oxide–opioid [6] and nitrous oxide–volatile agent [7] anaesthesia than those associated with thiopentone alone.

In this study the patients received only nitrous oxide and oxygen during the study period. Supplementary opioids and volatile agents were given when the study was complete. Vecuronium was chosen as the neuromuscular blocking drug as it has been shown to have virtually no cardiovascular effects [8]. These anaesthetic agents were selected to minimize changes in haemodynamic variables in order to highlight the effect of the induction agent on the cardiovascular system.

Both thiopentone and propofol in equipotent doses have been shown to have adverse cardiovascular effects, secondary to decreased cardiac output and peripheral vasodilatation. Propofol may be the more haemodynamically unstable of the two drugs [9, 10]. In contrast, etomidate has been shown to have a very stable cardiovascular profile when used for i.v. induction [11]. Furthermore, it has been suggested that etomidate potentiates the non-depolarizing blocking effects of pancuronium [12].

In conclusion, the results of this study suggest that the onset of neuromuscular block may be affected by the amount of muscle perfusion, which in turn can be affected by the choice of i.v. induction agent. If rapid intubation of the trachea is required with a non-depolarizing neuromuscular blocking drug, etomidate may be the induction agent of choice, because of its favourable haemodynamic characteristics.

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British Journal of Anaesthesia 1992; **69**: 447–450

DISPOSITION OF ALFENTANIL IN BURNS PATIENTS

A. G. MACFIE, A. D. MAGIDES AND C. S. REILLY

SUMMARY

We have studied the disposition of alfentanil in six patients (who had suffered 10–30% surface area burns 5–21 days previously) undergoing surgical debridement and grafting and compared the data with those from a control group of six patients matched for age, sex and weight undergoing body surface surgery of similar duration. Plasma samples were collected up to 480 min after an i.v. bolus of alfentanil 50 µg kg^{-1}. Drug concentrations were measured by radioimmunoassay and alfentanil binding to plasma proteins by equilibrium dialysis. The burns patients had significantly greater concentrations of alpha-1-acid glycoprotein (AAG) and smaller concentrations of albumin. The mean protein binding of alfentanil was 94.2 (SEM 0.05)% in the burns group and 90.7 (0.4)% in the control group (P = 0.004). There was a good correlation between AAG concentration and protein binding (r = 0.8). The volume of distribution and total clearance of alfentanil were reduced significantly in the burns group. The clearance of the unbound fraction and the elimination half-life of alfentanil were not decreased significantly. (Br. J. Anaesth. 1992; **69**: 447–450)

KEY WORDS

Analgesics: alfentanil. Pharmacokinetics: protein binding. Surgery: burns.

The pathophysiological changes of burns injury may alter the pharmacokinetic and pharmacodynamic responses to drugs by various mechanisms. Major burns injury to the skin is associated commonly with pathological changes in the patient's cardiovascular, respiratory, hepatic and renal function [1].

The disposition of drugs may be altered after a burns injury as a result of changes in the binding capacity of plasma proteins. Commonly, these include a significant reduction in the concentration of plasma albumin and an increase in the acute phase protein, alpha-1-acid glycoprotein (AAG) [2, 3]. Albumin [4] and AAG [5] are both important binding proteins in human plasma. The requirements for neuromuscular blocking drugs are increased in burns injury patients [6]. Increased protein binding of tubocurarine does occur, but the changes in dose requirements are probably caused by increased nicotinic acetylcholine receptor numbers.

Free plasma concentrations of imipramine are reduced in patients after severe burns injury as a result of increased binding by AAG. In contrast, free concentrations of diazepam are increased because of reduced binding by albumin [3].

Alfentanil is a synthetic opioid which is highly protein bound (> 90%); the binding is thought to be mainly to AAG [7]. Although alfentanil may be used to provide analgesia during anaesthesia for debridement and grafting of burns, the disposition of alfentanil in burns patients is not known.

We report the disposition and protein binding of alfentanil in patients with significant burns.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and written consent was obtained from all patients.

The pharmacokinetics of alfentanil after an i.v. bolus were measured in six patients 5–21 days after they sustained burns to 10–30% of body surface area. We also studied a control group of six patients matched for age, weight and sex undergoing elective body surface surgery of similar duration (table I).

Patients with evidence of hepatic or renal disease and those receiving drugs likely to affect liver enzyme function were excluded. Full haematological and biochemical screens were performed before operation (table II).

A standardized anaesthetic technique was used. All patients received temazepam 20 mg orally 1 h before surgery. Anaesthesia was induced with a sleep

TABLE I. *Patient characteristics for the burns and control groups (mean (range or* SD*))*

	Burns	Control
Age (yr)	38.2 (18–58)	38.2 (18–62)
Sex (M:F)	4:2	4:2
Weight (kg)	57.4 (9.8)	61.3 (8.1)
Dose (mg)	2.9 (0.5)	3.1 (0.4)
Duration of operation (min)	84.0 (21.9)	73.5 (12.3)
% Burn	19.7 (9.3)	

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TABLE II. *Preoperative biochemical and haematological investigations of the burns and control groups (mean* (SD)). **Significant difference between groups* (P < *0.05)*

	Burns	Control
Albumin (g litre^{-1})	31.8 (3.4)*	45.0 (2.7)
AAG (mg dl^{-1})	186.2 (24.7)*	93.5 (20.5)
Total protein (g litre^{-1})	57.0 (4.5)*	71.4 (5.2)
Haemoglobin (g dl^{-1})	12.8 (0.6)*	14.3 (0.9)
WBC × 10^9 ml^{-1}	9.7 (3.5)*	6.0 (1.5)
Platelets × 10^9 ml^{-1}	363.2 (37.9)	242.5 (32.9)
Sodium (mmol litre^{-1})	133.3 (3.0)*	137.5 (2.1)
Potassium (mmol litre^{-1})	4.7 (0.9)	3.9 (0.4)
Urea (mmol litre^{-1})	7.8 (6.1)	4.3 (1.2)
Creatinine (mmol litre^{-1})	101.0 (64.7)	89.8 (20.9)
ALT (mmol litre^{-1})	30.7 (19.0)	18.6 (10.7)
Bilirubin (mmol litre^{-1})	9.7 (10.0)	10.2 (3.8)

dose of thiopentone and tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1}. The lungs were ventilated to normocapnia with 66 % nitrous oxide and 0.5–1.0 % isoflurane in oxygen to maintain an adequate level of anaesthesia. The ECG, Sp_{O_2}, and E'_{CO_2} were measured continuously and arterial pressure was recorded non-invasively every 3 min.

Hartmann's solution was infused i.v. as a maintenance fluid and to replace blood losses up to 15 % of the blood volume. Only one patient required blood transfusion—during the postoperative period in a patient with a 20 % surface area burn.

After induction of anaesthesia, an i.v. bolus dose of alfentanil 50 µg kg^{-1} was given. Venous blood samples were obtained for measurement of alfentanil concentration in lithium–heparin tubes at 0, 2, 5, 10, 15, 30, 60 and 90 min and 2, 3, 4, 6, 7 and 8 h after administration of alfentanil. Blood samples were taken also at 0, 1 and 8 h for measurement of AAG concentration and alfentanil binding.

The venous blood samples were centrifuged and the plasma separated and stored at −20 °C for subsequent analysis. A radioimmunoassay technique using rabbit anti-alfentanil antibodies (lower limit of detection of 1 ng ml^{-1}) was used to measure alfentanil concentrations (CV intra-assay 7.5 %, inter-assay 11.6 %) at Janssen Pharmaceuticals, Belgium [8]. An equilibrium dialysis technique against sodium phosphate buffer 0.1 mol litre^{-1} at pH 7.4 and 37 °C was used to measure the protein binding of alfentanil, also at Janssen Pharmaceuticals [9].

The pharmacokinetic variables were calculated for each patient using both compartmental and non-compartmental models. The individual time–concentration curves were drawn from the alfentanil concentrations. The area under the curve (AUC) and area under the moment curve (AUMC) were calculated using the linear trapezoidal method. The apparent volume of distribution at steady state (V^{ss}) and the clearance (Cl) were calculated using standard non-compartmental formulae [10]. The elimination half-life ($T_{\frac{1}{2}}$) was calculated from individual time–concentration curves by linear regression of the last five concentrations. Clearance of the unbound fraction (Clu) was calculated from total drug clearance divided by unbound fraction. The compartmental variables were calculated by fitting the time–concentration data to a bi-exponential model and non-linear least squares regression using the programme PROC NONLIN, SAS.

Statistical analysis was undertaken using ANOVA (SPSS PC v3.0) and significance was taken at $P < 0.05$.

RESULTS

There was no significant difference between the groups in age, weight, sex ratio or duration of operation (table I). At the preoperative screening, the burns group had significantly smaller plasma albumin and total protein concentrations, a smaller haemoglobin concentration and greater white blood cell count (table II). There were no differences in the screening tests of renal and liver function, apart from a significantly smaller sodium concentration in the burns group.

The time–concentration curves for alfentanil in the two study groups are shown in figure 1. The burns group had significantly greater AAG concentrations and percentage of bound alfentanil. This represents a mean reduction of 40 % in the unbound fraction of alfentanil (table III).

V^{ss} and Cl were reduced significantly in the burns group. This effect was found using both compartmental and non-compartmental methods and there was no significant difference between the values calculated by the two methods within each group. However, the clearance of the unbound fraction of alfentanil was less in the burns group (21 ml min^{-1} compared with 29.3 ml min^{-1}), but this was not significant ($P = 0.07$). The mean elimination $T_{\frac{1}{2}}$ was greater in the burns patients at 305 min compared with 191 min ($P = 0.07$) using non-compartmental analysis and at 132 min and 76.9 min ($P = 0.12$), respectively, with compartmental analysis.

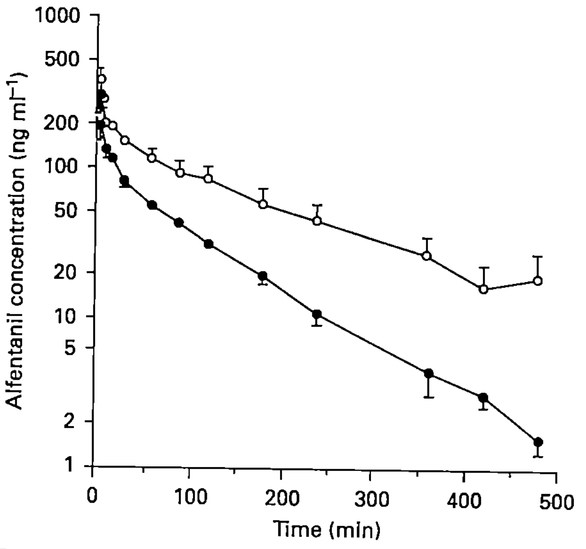

FIG. 1. Mean (SEM) plasma concentrations of alfentanil after an i.v. bolus of 50 µg kg^{-1} in the burns group (○) and the control group (●).

TABLE III. *Disposition and plasma protein binding of alfentanil in the burns and control groups (mean (SEM))*

	Burns	Control	*P*
AAG (mg dl^{-1})	186 (10)	94 (9)	0.004
% bound	94.2 (0.005)	90.7 (0.4)	0.004
Non-compartmental			
Cl (ml min^{-1})	125 (32)	256 (12)	0.005
V^{ss} (litre)	12.5 (0.8)	23.8 (1.3)	0.001
Elimination $T_{\frac{1}{2}}$ (min)	305 (50)	191 (11)	0.074
Clu (ml min^{-1})	21.6 (8)	29.3 (3)	0.07
Compartmental			
Cl (ml min^{-1})	119 (36)	273 (34)	0.016
V^{ss} (litre)	14.8 (0.6)	24.4 (1.6)	0.001
$T_{\frac{1}{2}}^{\alpha}$ (min)	4.7 (0.9)	3.7 (0.3)	0.37
$T_{\frac{1}{2}}^{B}$ (min)	132 (29)	77 (5)	0.13
A (ng ml^{-1})	343 (69)	407 (55)	0.51
α (min^{-1})	0.178 (0.004)	0.194 (0.015)	0.72
B (ng ml^{-1})	166 (11)	91 (8)	0.001
B (min^{-1})	0.0071 (0.0019)	0.0094 (0.0007)	0.32

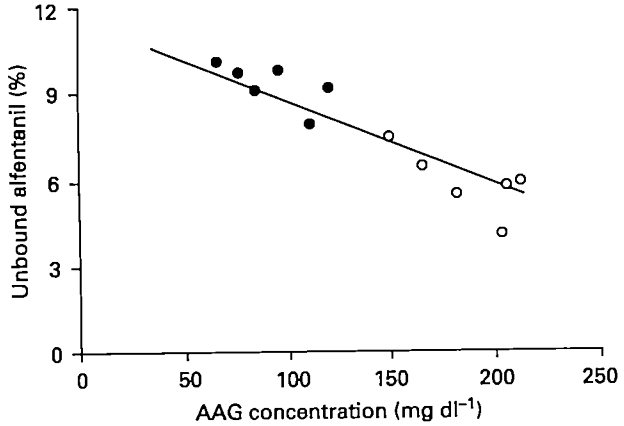

FIG. 2. Relationship of plasma concentrations of alpha-1-acid glycoprotein (AAG) and percent unbound alfentanil in the burns group (○) and the control group (●), showing the line of best fit ($r = 0.94$).

There was a good correlation ($r = 0.8$) between the AAG concentration and the percent unbound fraction of alfentanil for both groups (fig. 2).

DISCUSSION

We have shown that AAG concentrations were increased and the unbound fraction of alfentanil was reduced in the burns group compared with a matched control group. A good correlation was seen between AAG concentrations and the unbound alfentanil fraction. Martyn, Abernethy and Greenblatt suggested that drugs which are highly bound to albumin exhibit decreased binding, whereas drugs which are highly bound to AAG may show increased binding after burns injury [3]. This suggests that AAG was the major determinant of plasma protein binding of alfentanil and that changes in its concentration in association with burns injury resulted in increased binding.

The increase in AAG concentration in patients with burns injury may be up to 300% by day 8 and this returns to normal over 6–8 weeks [2]. Infective complications are often associated with major burns [11] and this may contribute to the increase in AAG concentration. This protein is found in increased concentrations also after myocardial infarction [12], renal transplantation, major surgery, malignancy, ulcerative colitis, Crohn's disease, infection, trauma and in the postoperative period [13]. Neonatal plasma AAG is reduced markedly compared with concentrations in adults [14].

AAG has been shown to be an important binding protein for several basic drugs including lignocaine, propranolol, imipramine, quinidine and bupivacaine [15]. It is likely that the disposition of other drugs is altered in a manner similar to that for alfentanil. Fentanyl may be extensively bound to AAG [16].

The change in volume of distribution may be explained by the change in binding. However, the decreased clearance and trend towards an increased elimination half-life suggest that the rate of removal of the drug from plasma is decreased by a separate mechanism in the burns patients. It is possible that changes in hepatic blood flow or hepatic enzyme activity may be produced as a result of the burns injury. It is possible also that the reduced volume of distribution and decrease in clearance imply that accumulation may occur after prolonged administration of alfentanil.

Drug effect is dependent on the free unbound drug concentration at the site of action. We did not compare the pharmacodynamic responses to alfentanil in the two groups in this study, but no gross differences were noted in the cardiovascular variables measured throughout anaesthesia and surgery.

This study demonstrates the significant effect that the change in AAG concentration had on the disposition of alfentanil in patients with burns injury. The effect of the acute phase reactant proteins on drug disposition may be of clinical significance in a variety of conditions, including burns injury, and may in part account for variations in patient response.

ACKNOWLEDGEMENT

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EFFECT OF DICLOFENAC ON RENAL FUNCTION AND PROSTACYCLIN GENERATION AFTER SURGERY

I. POWER, A. D. CUMMING AND G. C. PUGH

SUMMARY

We have examined the effect of diclofenac on renal function after major surgery in a randomized, double-blind, controlled study of 20 patients undergoing oesophagogastrectomy. Diclofenac 75 mg or placebo was given i.m. 12-hourly for 2 days. I.v. fluid administration was standardized. Renal function was assessed by fluid balance and measurement of serum creatinine and electrolyte concentrations, creatinine and free water clearance, and urinary sodium and potassium excretion. Urinary 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) was measured by radioimmunoassay to assess renal prostacyclin production. After surgery, 6-keto-$PGF_{1\alpha}$ production increased, but this did not occur with diclofenac. On the first day after surgery, use of diclofenac was associated with a decreased urine flow rate, decreased urinary sodium and potassium excretion and a tendency to hyperkalaemia. Frusemide was required more often in the diclofenac group. One patient was withdrawn from the diclofenac group because of impaired renal function. Urine flow rate and blood potassium concentration should be monitored if diclofenac is used after major surgery (Br. J. Anaesth. 1992; **69**: 451–456)

KEY WORDS

Analgesics: diclofenac. Hormones: prostaglandins, urinary 6-keto-$PGF_{1\alpha}$. Kidney: postoperative renal function.

The adverse renal effects of the non-steroidal anti-inflammatory analgesic drugs (NSAID) are serious and well described [1–6]. Most studies have examined the effect of long-term oral NSAID intake prescribed for medical conditions, but there is little work on the acute renal effects of short-term parenteral administration to surgical patients. It is known that animals are more sensitive to the renal effects of NSAID after laparotomy under general anaesthesia [7]. As the use of NSAID after surgery is becoming more common, it is important to identify a potential problem in man.

The kidney can synthesize most prostaglandins [8], and they act as local tissue hormones maintaining blood flow, regulating tubular processes involving electrolytes, and modulating the effect of other renal hormones [9]. The prostaglandins produced in greatest abundance by the kidney are prostacyclin (PGI_2) in the cortex and PGE_2 in the medulla [10]. Vasoconstrictor hormones, including renin, angiotensin, noradrenaline and vasopressin, produce a compensatory increase in the renal synthesis of vasodilator prostaglandins by inducing phospholipase [11], which breaks down membrane phospholipids to produce the chemical precursor of prostaglandins, arachidonic acid. In some clinical states associated with increased circulating concentrations of vasoconstrictors, which may include surgery, renal blood flow can become dependent on prostaglandins and NSAID may have acute adverse effects [1, 2].

It is our practice to use i.m. diclofenac in combination with local anaesthetics and i.v. morphine to provide analgesia after major thoracic surgery, including oesophagogastrectomy. Maintenance of correct fluid balance is important because overload may precipitate pulmonary oedema after thoracotomy in these, often malnourished, patients. This was thought to be an appropriate situation in which to investigate the effect of NSAID on postoperative renal function, especially as fluid balance is routinely monitored closely after oesophagogastrectomy.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee. Exclusion criteria were a history of peptic ulcer disease, asthma, previous reactions to NSAID, allergies, evidence of renal insufficiency based on preoperative venous blood sampling and biochemical analysis, diuretic therapy and recent NSAID ingestion. Twenty patients were enrolled after giving informed, written, consent and all had oesophagogastrectomy for carcinoma, performed via a left thoracoabdominal incision. The two drug groups were similar in age, height, weight, sex and surgical blood loss ($P = 0.6$) (table I).

A double-blind, randomized, controlled study of the effect of i.m. diclofenac on renal function after major surgery was performed. A control group was

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TABLE I. *Patients details (mean (range or SD) (†SE))*

	Diclofenac	Control
Age (yr)	65.2 (51–76)	69.8 (50–79)
Height (cm)	169.7 (9.9)	167.5 (8.4)
Weight (kg)	63 (17.2)	68.9 (15.7)
Sex (M:F)	9:1	8:2
Blood loss (ml)	500 (165†)	408 (58†)

included for comparison. Renal function and PGI_2 production were assessed on the day before operation, the day of surgery (day 1), and the day after surgery (day 2). Patients were allocated randomly to receive five i.m. injections of either diclofenac 75 mg or identical placebo. The injections were given at induction of anaesthesia, and 12-hourly thereafter.

The general anaesthetic technique was standardized. Premedication comprised i.m. papaveretum and atropine, anaesthesia was induced with i.v. propofol, suxamethonium was used to facilitate tracheal intubation, the lungs were ventilated with enflurane and nitrous oxide in oxygen and neuromuscular block was maintained with atracurium. At the end of the procedure, neuromuscular block was antagonized with neostigmine and atropine.

Intercostal nerve blocks were performed on each patient before surgery (40 ml of 0.5 % bupivacaine with adrenaline). All patients were given morphine by continuous i.v. infusion at a rate of 1 mg h^{-1} after operation and additional i.v. morphine was available at the discretion of one nurse observer. The patients were nursed in a high dependency unit during the study, and each completed a 100-mm visual analogue scale (VAS) for pain intensity (0 = no pain to 100 mm = worst possible pain) on a daily basis, according to normal ward practice.

In the operating theatre, central venous, arterial and urinary catheters were placed to allow routine monitoring and collection of blood and urine samples in the postoperative period.

Fluid therapy was standardized. Surgical blood loss was replaced in the operating theatre with plasma protein solution and normal saline. After surgery, normal saline and 5 % glucose were infused alternately at a rate of 500 ml every 6 h. Central venous pressure was maintained at 5–10 cm H_2O by the infusion of plasma protein solution.

Before operation, venous blood samples were analysed for creatinine and electrolyte concentrations. On the day before surgery, urine was collected from the time of enrolment into the study. In the postoperative period, urine output was measured for 48 h from the time of induction of anaesthesia.

Venous blood samples were taken on the day of surgery (day 1), and the next day (day 2), centrifuged at 2000 *g* and the plasma removed. Aliquots of the urine collection from each day were stored with the plasma samples at −20 °C for batch analysis at the end of the study using routine laboratory methods.

Plasma and urine concentrations of creatinine and electrolytes, and osmolality were examined in both groups over the 3-day study period. Urine flow rate, urinary excretion of sodium and potassium, and creatinine and free water clearances were calculated.

It was the practice in the surgical unit involved to give i.v. frusemide 10 mg if urine flow rate was less than 30 ml h^{-1} for two consecutive periods of 1 h. In this study, the number of patients in each group given frusemide were compared.

Previous studies have shown that the renal production of prostacyclin, PGI_2, can be assessed by measuring the concentration of the product of spontaneous hydrolysis, 6-keto-$PGF_{1\alpha}$, which is stable in urine but in blood is metabolized further to 2,3 dinor 6-keto-$PGF_{1\alpha}$ [12–14]. In this investigation, urinary 6-keto-$PGF_{1\alpha}$ was measured in aliquots of the preoperative collection and of the two 24-h urine volumes collected after surgery. Knowing the urinary volume produced in a given time, we were able to calculate the production per minute of 6-keto-$PGF_{1\alpha}$.

Measurement of 6-keto-$PGF_{1\alpha}$ was by radioimmunoassay as described previously [15]. Briefly, aliquots of urine were collected and stored at −20 °C until the analysis was performed in a batch. After thawing, urine was acidified and the prostaglandin extracted into ethyl acetate. The assay used a double-antibody technique as the separation method. The specific antibody for 6-keto-$PGF_{1\alpha}$ was raised in the Department of Pharmacology of the University of Edinburgh, and tritiated 6-keto-$PGF_{1\alpha}$ was obtained from Amersham International Ltd. The inter-assay and intra-assay coefficients of variation were 15 % and 11 %, respectively.

Statistical analysis

At the end of the study, the randomization code was broken and the two groups compared. Patient details are given as mean (SD), and other values as mean (SE). The two treatment groups were compared on the day before operation, and on the first (day 1) and second (day 2) days after surgery. Changes in individuals from baseline were examined using analysis of variance and paired *t* tests. Comparisons between the diclofenac and morphine groups were made using unpaired *t* tests. Categorical data (whether or not the patient was given frusemide) were analysed using a chi-square test. The significance level was set at 5 % and, where appropriate, 95 % confidence intervals (95 % CI) were calculated.

RESULTS

Before surgery, there was no significant difference between the groups in plasma electrolyte concentrations, urine output, electrolyte excretion, creatinine clearance, or 6-keto-$PGF_{1\alpha}$ production (table II).

Plasma concentrations of sodium, potassium and creatinine, and osmolality (table II). There was no significant difference between the diclofenac and placebo groups at any time, although the diclofenac group tended to have greater potassium concentrations than the control group on the first day after operation: five of the diclofenac group had potassium concentrations in excess of the laboratory upper limit of normal (4.7 mmol $litre^{-1}$) and in three the concentrations were greater than 5 mmol $litre^{-1}$. In comparison, only two patients in the control group had increased potassium concentrations on day 1,

TABLE II. *Plasma concentrations of sodium, potassium and creatinine, and osmolality (mean (SE)). P: unpaired t test*

	Diclofenac	Control	P
Sodium (mmol litre^{-1})			
Before op.	138 (1)	138 (2)	0.95
Day 1	136 (1)	136 (2)	0.9
Day 2	135 (2)	135 (2)	0.9
Potassium (mmol litre^{-1})			
Before op.	4.4 (0.2)	4.1 (0.1)	0.2
Day 1	4.6 (0.3)	4.2 (0.2)	0.2
Day 2	4.3 (0.2)	4.3 (0.1)	0.8
Creatinine (µmol litre^{-1})			
Before op.	89 (5)	89 (7)	0.95
Day 1	99 (12)	106 (13)	0.69
Day 2	104 (16)	98 (14)	0.77
Osmolality (mosmol kg^{-1})			
Before op.	282 (2)	284 (3)	0.7
Day 1	281 (3)	278 (4)	0.5
Day 2	279 (4)	276 (4)	0.58

and none exceeded 5 mmol litre^{-1}. Potassium concentrations in the diclofenac group returned towards normal by day 2.

In the control group, there was a significant reduction from preoperative values in plasma sodium concentration on day 1 ($P = 0.03$, 95%CI -7 to -0.04 mmol litre^{-1}) and plasma osmolality on days 1 and 2 ($P = 0.07$, 95%CI -13 to 0.6 mosmol kg^{-1}, and $P = 0.03$, 95%CI -18 to -2 mosmol kg^{-1}). In the diclofenac group, the only significant change was that plasma sodium concentration decreased from preoperative values on day 1 ($P = 0.05$, 95%CI -5 to 0 mmol litre^{-1}).

Fluid balance (table III). There was no significant difference in the amount of i.v. fluids given to the two groups on day 1 or day 2 ($P = 0.9$ and 0.5, respectively). The diclofenac group tended to have a greater positive fluid balance on the first day after operation, although the difference was not statistically significant.

Urine output (table III). Urine production was significantly less in the diclofenac group on day 1 compared with the control group ($P = 0.02$, 95%CI -0.5 to -0.06 ml min^{-1}). On day 2, there was no significant difference between the groups.

Sodium and potassium excretion (table III). Urinary excretion of sodium was significantly less in the diclofenac group on day 1 ($P = 0.01$, 95%CI -62 to -8 µmol min^{-1}). Potassium excretion increased in both groups in the postoperative period, but the increase was greater in the control group on day 1, so that potassium excretion was less in the diclofenac group on that day ($P = 0.04$, 95%CI -49 to -1 µmol min^{-1}) On day 2, there was no statistically significant difference between the groups.

Creatinine clearance (table III). Preoperative creatinine clearances were not significantly different in the two groups. In the control group, there was a significant increase in creatinine clearance on day 1 ($P = 0.02$, 95%CI 6–53 ml min^{-1}), but there was no change in the diclofenac group.

Free water clearance (table III). There was a statistically significant difference between the groups only on day 1, when the control group retained more free water than the diclofenac group ($P = 0.04$, 95%CI 0.01–0.8 ml min^{-1}).

Urinary 6-keto-PGF$_{1\alpha}$ (fig. 1, table IV). Urinary excretion of 6-keto-PGF$_{1\alpha}$ increased markedly in the control group after surgery, especially on day 1. In contrast, the diclofenac group showed little change.

TABLE III. *Effect of diclofenac on fluid balance, urine output, urinary sodium and potassium excretion, and creatinine and free water clearance (mean (SE)). P: unpaired t test*

	Diclofenac	Control	P
Fluid balance (ml)			
Day 1	1128 (348)	601 (127)	0.39
Day 2	1569 (275)	1532 (233)	0.93
Urine output (ml min^{-1})			
Before op.	0.75 (0.1)	0.89 (0.1)	0.27
Day 1	0.62 (0.06)	0.88 (0.13)	0.02
Day 2	0.9 (0.1)	0.98 (0.16)	0.65
Sodium excretion (µmol min^{-1})			
Before op.	63 (14)	75 (10)	0.51
Day 1	43 (9)	78 (8)	0.01
Day 2	37 (9)	48 (11)	0.5
Potassium excretion (µmol min^{-1})			
Before op.	22 (3)	19 (4)	0.73
Day 1	49 (6)	74 (9)	0.04
Day 2	39 (3)	41 (7)	0.76
Creatinine clearance (ml min^{-1})			
Before op.	61 (10)	60 (7)	0.97
Day 1	62 (13)	89 (14)	0.17
Day 2	62 (11)	77 (11)	0.38
Free water clearance (ml min^{-1})			
Before op.	-0.2 (0.2)	-0.1 (0.2)	0.15
Day 1	-0.5 (0.1)	-1.0 (0.2)	0.04
Day 2	-0.3 (0.1)	-0.2 (0.3)	0.7

TABLE IV. *Effect of diclofenac on the urinary excretion of 6-keto-PGF$_{1\alpha}$ (mean (SE)). P: unpaired t test*

	6-Keto-PGF$_{1\alpha}$ excreted (pg min^{-1})		
	Diclofenac	Control	*P*
Before op.	532 (120)	338 (78)	0.2
Day 1	587 (85)	5111 (1553)	0.02
Day 2	379 (65)	1739 (336)	0.003

TABLE V. *Details of the patient withdrawn from the diclofenac group on day 1*

	Before op.	Day 1	Day 2
Sodium (mmol litre^{-1})	138	138	136
Potassium (mmol litre^{-1})	4.6	5.4	4.5
Creatinine (μmol litre^{-1})	101	158	145
Osmolality (mosmol kg^{-1})	278	292	289
Creatinine clearance (ml min^{-1})	45	25	26
6-keto-PGF$_{1\alpha}$ (pg min^{-1})	262	725	1455

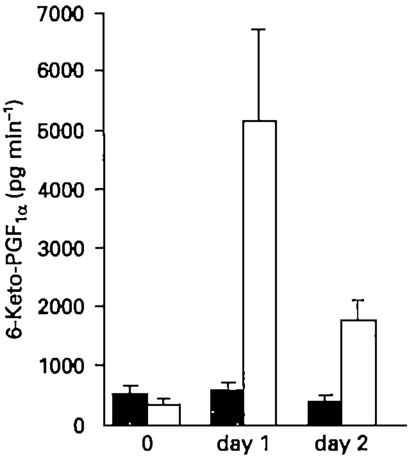

FIG. 1. Urinary excretion of 6-keto-PGF$_{1\alpha}$ for the diclofenac (■) and control (□) groups on the three study days (mean (SE)). O = Before operation.

Consequently, urinary 6-keto-PGF$_{1\alpha}$ excretion was significantly greater in the control group on days 1 and 2 ($P = 0.02$ and 0.003, respectively).

Frusemide. Diuretic therapy was required more often after surgery in the diclofenac group; nine patients were given frusemide, in comparison with only four in the control group ($P = 0.02$).

Analgesia. There was no significant difference between the pain scores of the two groups during the study. For example, on the day after operation the mean VAS scores were 27(9) mm and 31(8) mm ($P = 0.8$) for the control and diclofenac groups, respectively. The control group, however, required more morphine during the study (62(5.3) mg) than the diclofenac group (49(7.7) mg), although this difference was not significant ($P = 0.2$, 95 %CI −7 to 32 mg).

Adverse events (table V). One patient in the diclofenac group was withdrawn from the study after 18 h because of concern about persistently small volumes of urine (averaging less than 20 ml h^{-1}). Two doses of diclofenac had been given before the patient was withdrawn. Despite adequate fluid loading and frusemide administration, i.v. dopamine was required to promote an acceptable urine flow. After withdrawal of diclofenac and commencement of dopamine, renal function improved and the patient recovered completely. Blood analysis revealed a marked increase in creatinine and potassium concentration on day 1. Plasma potassium concentration on day 1 was particularly great—5.4 mmol litre^{-1} (laboratory upper limit of normal 4.7 mmol litre^{-1}). It should also be noted that, although the preoperative creatinine concentration was within normal limits (55–150 μmol litre^{-1}), this patient had a reduced preoperative creatinine clearance (45 ml min^{-1}) which decreased by almost 50 % on the first day after operation. In contrast to the pattern found in the control patients, urinary 6-keto-PGF$_{1\alpha}$ continued to increase in this patient from day 1 to day 2, after diclofenac was withdrawn.

DISCUSSION

Urinary 6-keto-PGF$_{1\alpha}$ production increased markedly in the postoperative period in the control group, whereas there was no change with diclofenac (fig. 1, table IV). Urinary 6-keto-PGF$_{1\alpha}$ is an accepted indicator of renal PGI$_2$ production [12–14]. To our knowledge, this is the first report of such an increase in renal PGI$_2$ production after surgery in humans, and of the effect of diclofenac.

Prostaglandins are thought to act as local vasodilators which maintain renal function in clinical conditions associated with large concentrations of circulating vasoconstrictors (e.g. congestive cardiac failure, hypovolaemia), when blood flow can become "prostaglandin dependent" [1, 2]. On the basis of this study, it may be that renal prostaglandins are important after surgery. As renal PGI$_2$ production peaked on the first day after operation in the control group, this effect may be most important in the immediate postoperative period.

As there is inevitably tissue damage and disruption after oesophagogastrectomy, which could release many factors including prostaglandins, it should be established that the urinary 6-keto-PGF$_{1\alpha}$ measured in this study did represent renal, not systemic, PGI$_2$ production. There is no published work on the effect on anaesthesia and surgery on urinary metabolites of PGI$_2$, but studies have been reported on plasma 6-keto-PGF$_{1\alpha}$, which may reflect systemic production of PGI$_2$ to some extent. Minor surgery does not increase plasma 6-keto-PGF$_{1\alpha}$, whether using general [16], or spinal [17] anaesthesia. Plasma 6-keto-PGF$_{1\alpha}$ concentration increases after surgical incision of laparotomy, but decreases within 40 min [18], and this is prevented by pretreatment with ibuprofen [19]. Such studies indicate that systemic PGI$_2$ production is not increased greatly after surgery. The increase in urinary 6-keto-PGF$_{1\alpha}$ observed in this study may therefore truly reflect an increase in renal PGI$_2$ production after major surgery. In order to investigate this further, it would be useful to observe simultaneously both urinary 6-keto-PGF$_{1\alpha}$ and 2,3 dinor 6-keto-PGF$_{1\alpha}$ (the final urinary excretion metabolite of systemic PGI$_2$ production) after surgery to represent production of renal and systemic PGI$_2$, respectively, as used in recent studies of other clinical problems [14].

In this study, diclofenac therapy was associated with significantly reduced urine flow and sodium and potassium excretion on the first day after operation, but on the next day there was no difference (table III). Renal prostaglandins increase urinary sodium excretion [20, 21], and diclofenac could have produced sodium retention by inhibiting this. PGI$_2$ stimulates renin release in man [22] and, by preventing this, diclofenac could have impaired potassium excretion. In the postoperative period there is presumably a significant potassium load presented to the kidneys, which has to be excreted to avoid hyperkalaemia.

Creatinine clearance may not be a reliable indicator of glomerular filtration rate after surgery, when plasma creatinine concentrations could be changing as a result of muscle damage. Indeed, creatinine clearance increased in the control group after operation. Inulin and para-amino hippuric acid clearance studies may be more useful.

Because NSAID potentiate vasopressin [2, 9, 11, 23] it may have been expected that the diclofenac group would retain more fluid, but in fact the control group conserved more free water on the first day after operation (table III). This was reflected in the tendency for plasma osmolality to decrease in the control group (table II). Other factors, including pain intensity and morphine administration, may be involved, as they are known to increase vasopressin release.

Frusemide was given more often to patients in the diclofenac group. Although it would have been desirable to control the administration of diuretics during the study, in practice it was not possible to do so. The observed differences between the groups in urine flow and electrolyte excretion may have been even greater if frusemide had not been given.

Although diclofenac impaired renal function on the first day after surgery, the results of this study indicate that this effect was short lived. Urine output, urinary sodium and potassium excretion and free water clearance were not significantly different with diclofenac on the second day after surgery (table III), although renal PGI$_2$ production was still inhibited by diclofenac at that time (fig. 1, table IV). This may indicate that renal prostaglandins are involved in maintaining renal function for perhaps up to 1 day after surgery, but thereafter their importance may be diminished. Consequently, any adverse renal effects of NSAID given during surgery may be expected to occur in this period. It may be prudent to avoid the use of NSAID if there is a significant risk of intraoperative haemorrhage, as renal prostaglandins may be especially important in maintaining kidney function during episodes of hypotension.

The patient withdrawn from the study had marked impairment of renal function which became obvious after only two doses of diclofenac (table V). Although this patient had a normal preoperative plasma creatinine concentration (101 μmol litre^{-1}), subsequent analysis revealed that creatinine clearance was reduced (45 ml min^{-1}), suggesting that there was pre-existing renal impairment. Creatinine clearance is not measured routinely in such patients before surgery, and in this work the result was analysed only after completion of the study. The deterioration in renal function seen in this patient may have resulted from diclofenac, as it was similar to the effect seen when NSAID were given to patients with mild, asymptomatic renal failure [4]. This emphasizes the importance of monitoring renal function when NSAID are given to patients at risk of adverse events, with subclinical renal impairment, despite normal blood concentrations of creatinine. The patients in this study were elderly, and had major surgery for a debilitating disease. It is likely that this group would be particularly susceptible to NSAID-induced renal toxicity [5].

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MECHANISM OF EXTENSION OF SPINAL ANAESTHESIA BY EXTRADURAL INJECTION OF LOCAL ANAESTHETIC

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SUMMARY

We have examined the effect of extradural injection of 0.5% bupivacaine or normal saline on the progression of spinal anaesthesia in 28 patients undergoing Caesarean section. Three groups were studied. Subarachnoid anaesthesia was established in all patients. Group A (n = *10), the control, received no extradural injection for 20 min. Group B* (n = *9) received extradural bupivacaine 10 ml and group C* (n = *9) received extradural saline 10 ml 5 min after the subarachnoid injection. Sensory levels were compared at 5-min intervals and extension of the block was found to be similar in groups B and C and significantly faster than the control* ($P < 0.05$)*. The quality of anaesthesia and incidence of adverse effects was similar for all three groups. We conclude that the mechanism of extension of spinal anaesthesia by extradural injection of local anaesthesia is largely a volume effect.* (Br. J. Anaesth. 1992; **69**: 457–460)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques, regional: extradural, spinal.

The combined spinal–extradural technique of providing regional anaesthesia for Caesarean section is becoming increasingly popular. Subarachnoid injection of local anaesthetic provides rapid onset and reliable sacral block, whilst the presence of an extradural catheter allows flexibility in extending the block and provision of postoperative analgesia [1–4].

The injection of a relatively small amount of 0.5% bupivacaine into the extradural space after a subarachnoid injection of a standard dose of bupivacaine results in rapid extension of the block [5, 6]. Both the degree and speed of onset of this extension cannot be adequately explained solely by the presence of a small volume of local anaesthetic within a localized area of the extradural space.

Several hypotheses have been advanced to explain this enhancement of the subarachnoid block. These include leakage of extradural bupivacaine into the subarachnoid space via the hole created by the subarachnoid puncture, the existence of a "subclinical" analgesia at a higher level which is enhanced and becomes evident by perineural or transdural spread of the extradural solution, or the continuing spread of the initial subarachnoid injection independent of the extradural injection [4–7].

The extradural injection, by causing compression of the subarachnoid space and spread of the local anaesthetic within, may be another mechanism to explain this effect. This study was designed to compare the effect of extradural injection of normal saline or bupivacaine with a control group receiving no extradural injection on the level of the subarachnoid block.

PATIENTS AND METHODS

We studied 28 patients undergoing elective Caesarean section under regional anaesthesia. All were at term and none had any medical or obstetric complications. The investigation was approved by the Ethnics Committees of Newcastle and South Tees Health Authorities and informed consent was obtained from all patients.

All patients received oral ranitidine 150 mg 2 h before operation, 30 ml oral sodium citrate 0.3 mol litre^{-1} on leaving the ward and a standard preload of 1500 ml of warmed Hartmann's solution i.v. With the patient sitting, the extradural space was located via the L2–3 or L3–4 interspace with a 16-gauge Tuohy needle (Portex), using loss of resistance to air. A 26-gauge spinal needle was inserted through the Tuohy needle and the subarachnoid space identified by the appearance of CSF at the hub of the needle. Using a technique similar to that described by Rawal [6], 0.5% hyperbaric bupivacaine was injected—1.6 ml if the patient was less than 163 cm tall and 1.8 ml if they were 163 cm or taller. The spinal needle was removed and a catheter inserted 3 cm into the extradural space.

The patient was then placed supine with a 15° left tilt. Care was taken to avoid caval compression as this has been shown to influence the spread of subarachnoid local anaesthetic [8, 9]. An i.v. bolus of ephedrine 6 mg was given as prophylaxis against hypotension. Oxygen was administered by face mask and ECG, Sp_{O_2} and arterial pressure monitored throughout the time of the study.

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TABLE I. *Patient characteristics and surgical details (mean (range or SD)). No significant difference between groups*

	Group A (Control) ($n = 10$)	Group B (Bupivacaine) ($n = 9$)	Group C (Saline) ($n = 9$)
Age (yr)	28.6 (21–37)	29.8 (22–35)	28.7 (22–42)
Weight (kg)	74.7 (5.7)	69.3 (6.7)	74.0 (7.3)
Height (cm)	161.8 (6.0)	163.4 (6.6)	162.6 (4.3)
Time to start of surgery (min)	36.5 (4.7)	32.2 (2.6)	31.7 (2.5)
Duration of surgery (min)	50.0 (4.1)	46.7 (5.0)	45.6 (9.2)
Time to first request for analgesia (min)	162.5 (48.7)	133.89 (22.3)	156.1 (64.0)

The patient was then allocated randomly to one of three groups: group A (control; 10 patients): no extradural injection within 20 min after the subarachnoid injection; group B (bupivacaine; nine patients): extradural injection of 0.5 % bupivacaine 10 ml 5 min after the subarachnoid injection; group C (saline; nine patients): extradural injection of normal saline 10 ml 5 min after the subarachnoid injection.

The extradural injection of 10 ml at the 5-min interval was administered over 20 s by an operator blinded to the composition of the injection. Twenty minutes after the subarachnoid injection, the level of sensory block was extended to T4 or T5 by extradural injection of 0.5 % bupivacaine if required.

The level of sensory block was tested by pinprick every 5 min and at the time of the first incision. Motor function in the lower limbs was tested at 5-min intervals and graded according to the Bromage classification (grade 4 = full power; grade 1 = no power) [10].

If the patient experienced pain or discomfort, analgesia was supplemented with one or more i.v. boluses of alfentanil, progressing to general anaesthesia if required. Surgical analgesia was assessed by the anaesthetist and graded as excellent if no supplementation was required, good if one dose of alfentanil was administered with good effect, fair if more than one dose was required or poor if general anaesthesia was necessary. The patient was asked to grade her experience subjectively on the same scale.

Any adverse event during operation was recorded. Hypotension was defined as a systolic arterial pressure less than 100 mm Hg or a decrease of 30 % from baseline value, and was treated with 6-mg i.v. boluses of ephedrine.

The condition of the baby was assessed at birth and 5 min (Apgar score).

After operation, time to first request for analgesia was noted and the woman questioned about the presence of backache, headache, urinary problems and any delay in mobilization. Patients were asked if they would choose the technique again.

Statistical analysis was performed using the Fisher exact, Mann–Whitney U and Student's t tests as appropriate. Significance was assumed at the 5 % level ($P < 0.05$).

RESULTS

The three groups were comparable in age, weight and height (table I).

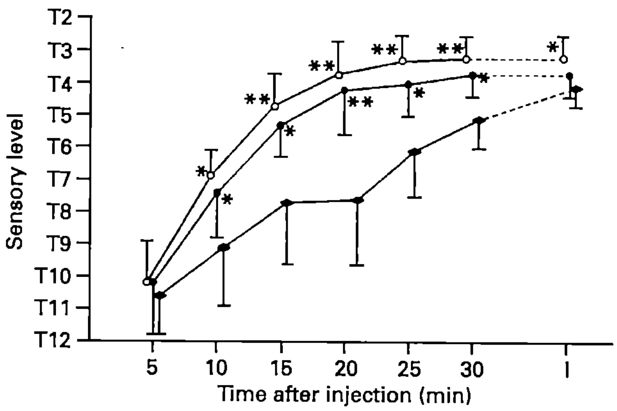

FIG. 1. Onset of sensory block (mean, SD). Group A, control (◆) received extradural bupivacaine at 20 min; group B (●) received extradural bupivacaine at 5 min; group C (○) received extradural saline at 5 min. I = First incision. $^*P < 0.05$; $^{**}P < 0.01$ compared with control. No significant difference between groups B and C.

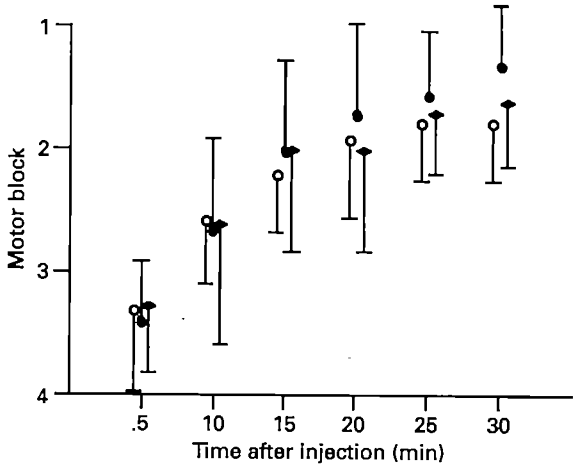

FIG. 2. Onset of motor block (mean, SD) (Bromage scale). Group A, control (◆) received extradural bupivacaine at 20 min; group B (●) received extradural bupivacaine at 5 min; group C (○) received extradural saline at 5 min. No significant difference between groups.

Levels of sensory blocks during operation are shown in figure 1. At 5 min, the levels in the three groups were similar. Progression of the level was rapid in both groups receiving extradural injections at 5 min and was significantly slower in the control group and had stabilized by 20 min. At this time, eight patients in group A, two in group B and one in

TABLE II. *Total doses of bupivacaine and volumes injected into the extradural space (mean (SD) [range]).* *$P < 0.05$ *significant difference compared with control*; **$P < 0.01$ *significant difference compared with group B*

	Group A (Control) ($n = 10$)	Group B (Bupivacaine) ($n = 9$)	Group C (Saline) ($n = 9$)
Subarachnoid bupivacaine (mg)	8.5 (0.5)	8.7 (0.5)	8.4 (0.3)
Extradural bupivacaine (mg)	30.5 (21.2) [0–65]	54.4 (9.2) [50–75]*	1.7 (5.0) [0–15]* **
Extradural volume (ml)	6.1 (4.2)	10.9 (1.8)*	10.3 (1.0)*
Final sensory level (thoracic dermatome)	4.1 (0.6)	3.7 (0.7)	3.2 (0.7)*

TABLE III. *Incidence of adverse events. No significant difference between groups*

	Group A (Control) ($n = 10$)	Group B (Bupivacaine) ($n = 9$)	Group C (Saline) ($n = 9$)
Hypotension	2	4	5
Pain	1	0	1
Discomfort	3	3	2
Nausea	1	2	2

TABLE IV. *Quality of anaesthesia (see text). No significant difference between groups*

	Group A (Control) ($n = 10$)	Group B (Bupivacaine) ($n = 9$)	Group C (Saline) ($n = 9$)
Anaesthetist			
Excellent	6	6	5
Good	2	2	2
Fair	1	1	2
Poor	1	0	0
Patient			
Excellent	6	6	5
Good	3	2	3
Fair	0	1	1
Poor	1	0	0

group C required further extradural bupivacaine to extend the block to T4 or T5 ($P < 0.05$).

The degree of motor block (fig. 2) was not related to height of sensory block or speed of progression and there was no significant difference between the groups.

The saline group received significantly less extradural bupivacaine to achieve comparable sensory levels, the final sensory level being related closely to the volume injected into the extradural space (table II).

Time to the first incision, duration of surgery and time to first request for analgesia were similar for all three groups (table I).

The incidence of adverse events is summarized in table III. Hypotension occurred more frequently in groups B and C (ns).

The number of patients requiring alfentanil supplementation was similar in all groups (table IV). One patient in the control group, despite having loss of pinprick sensation to T4, required general anaesthesia because of severe pain.

All babies were vigorous at birth and had an Apgar score of 8 or more at 5 min.

After operation, there was no difference between the groups in the incidence of backache, headache, urinary problems and delay in mobilization. No post-spinal headaches occurred. One patient in the control group would not choose the same technique again.

DISCUSSION

It is well recognized that alterations in the contents of the spinal canal can influence the spread of local anaesthetic. It is thought that one of the reasons for the pregnant patient's decresed requirement of local anaesthetic agent for spinal anaesthesia in the latter stages of gestation is an increased vertebral venous volume and a reciprocal decrease in CSF volume at the caudal end of the subarachnoid space [7–9]. Compression of the inferior vena cava in non-pregnant patients, causing vertebral venous engorgement, increases the spread of subarachnoid local anaesthetic [8]. It has been shown that spread of subarachnoid local anaesthesia is slow in pregnant patients who are kept in the lateral position, with rapid progression when turned into a supine wedged position [11]. Hilt, Gramm and Link noted increases in intracranial pressure in head injured patients receiving lumbar extradural injection of local anaesthetic and similar increase with extradural injection of saline [12].

The evidence would suggest that compliance within the vertebral canal is dependent on a balance between vertebral blood volume and CSF volume. The injection of local anaesthetic or of any other fluid into the extradural space may be expected to result in initial shifts of one or both of these components before the fluid leaks away via the intervertebral foramina or is absorbed into the blood stream or CSF.

It has been noted that relatively small doses of extradural local anaesthetic, injected in the lumbar region, are required to extend a "fixed" subarachnoid block from T8 to T3–4 [5, 6]. The short space of time in which the extension occurs suggests a mechanism other than diffusion of the anaesthetic into the CSF or block of nerve roots within the extradural space.

This study has shown that rapid extension of spinal anaesthesia is possible by injecting either local anaesthetic or saline into the lumber extradural space. We postulate that the rapidity of extension is caused by increased volume within the extradural space, causing a decrease in CSF volume in the caudal subarachnoid space and cephalad shift of local anaesthetic within the CSF.

Time from injection of local anaesthetic to commencement of surgery was in excess of 30 min. In groups B and C this was partly, but not entirely, the result of the requirements of the study. For the purposes of the study, we used a technique similar to that described by Rawal, Schollin and Wesström [6], injecting a small amount of local anaesthetic to patients placed in the sitting position, and deliberately aiming to achieve inadequate anaesthesia which was extended higher by the extradural. It is our usual practice to inject 0.5% hyperbaric bupivacaine 2.5 ml into the CSF and we seldom need to extend the block with extradural anaesthetic. This results in a more rapid achievement of surgical anaesthesia and we would agree with Carrie [5] that this is preferable.

The incidence of adverse events was similar to that which may be expected for any regional technique for Caesarean section.

The need for opioid supplementation of analgesia was similar for all three groups and amounted to 40% of all patients studied. This compares poorly with the findings of Rawal, Schollin and Wesström (13%), who found the combined spinal–extradural techique better than extradurals alone [6] and is more in keeping with the findings of Alahuhta and colleagues, who showed an incidence of visceral pain of 50% for both spinal and extradural techniques for Caesarean section [13]. In our own experience, combined spinal and extradurals using 0.5% hyperbaric bupivacaine 2.5 ml results in a lower incidence of visceral pain [unpublished observations].

In this study we have shown that subarachnoid anaesthesia may be extended as effectively with extradural injection of normal saline as with bupivacaine. It remains to be seen if the block can be extended if saline is injected at 20 min. This would provide important benefits, namely reducing the total local anaesthetic dose and obviating the need for a test dose which, at that time, would be difficult to interpret.

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COMPARISON OF HYPERTONIC SALINE (5%), ISOTONIC SALINE AND RINGER'S LACTATE SOLUTIONS FOR FLUID PRELOADING BEFORE LUMBAR EXTRADURAL ANAESTHESIA†

P. VEROLI AND D. BENHAMOU

SUMMARY

We have compared the haemodynamic effects of fluid preloading performed before lumbar extradural anaesthesia with isotonic saline (NS), 5% hypertonic saline (HS) and Ringer's lactate (RL) solutions in 30 ASA I patients undergoing minor orthopaedic surgery, allocated randomly to the three groups. All patients received an equal amount of sodium (2 mmol kg^{-1}). After fluid preloading, lumber extradural anaesthesia was performed (2% lignocaine 6 mg kg^{-1}) and ephedrine was administered in order to maintain mean arterial pressure (MAP) > 80% of its control value. Both volume and duration of fluid preload were significantly less in group HS (160 (SD 25) ml, 8.8 (SD 2.9) min) than in the two other groups (NS: 903 (144) ml, 17.7 (3.3) min; RL: 932 (166) ml, 212 (6.0) min) (P < 0.05). The number of blocked segments and the total amount of ephedrine administered were similar in the three groups. Heart rate increased significantly in all groups immediately after the fluid preload and remained increased until the end of the study (90 min). MAP was not affected by any fluid preload and its maximal decrease after lumbar extradural anaesthesia was similar in all groups. Infusion of 5% HS 2.3 ml kg^{-1} was tolerated well and produced a significant (P < 0.05) but moderate hypernatraemia lasting 90 min after the end of fluid preloading. We conclude that HS may be useful when rapid fluid preloading is desired, in situations where excess free water administration is not desired. (Br. J. Anaesth. 1992; **69**: 461–464)

KEY WORDS

Anaesthetic techniques: extradural, fluid preloading. Fluid balance: hypertonic saline, isotonic saline, Ringer's lactate.

Lumbar extradural anaesthesia may induce arterial hypotension as a result of a sympathetic nerve block [1]. Although haemodynamic effects induced by the technique are usually tolerated well in healthy young patients [2], prevention of hypotension is commonly achieved using fluid preloading. Anaphylactic reactions may occur after the administration of colloids; this risk is rare, but may not be acceptable for prophylaxis. Ringer's lactate solution (RL) is the solution used most commonly for fluid preloading [2], even though its sodium concentration (130 mmol litre^{-1}) is less than that in 0.9% isotonic sodium chloride solution (NS) (155 mmol litre^{-1}). Hypertonic saline solutions have been used effectively for fluid resuscitation in haemorrhagic shock [3, 4], during surgical treatment of aortic aneurysm [5] and for postoperative fluid therapy after coronary artery bypass grafting [6]. However, hypertonic saline (HS) has not been evaluated for fluid preloading before lumbar extradural anaesthesia.

The present study was undertaken to evaluate and compare, in a randomized double-blind study, the haemodynamic effects of fluid preloading performed before lumbar extradural anaesthesia with hypertonic saline, Ringer's lactate and isotonic saline solutions.

PATIENTS AND METHODS

After informed consent and local Ethics Committee approval were obtained, we performed a prospective double-blind study in 30 ASA physical status I adult patients undergoing lower limb orthopaedic surgery with tourniquet under lumbar extradural anaesthesia. After an overnight fast, all patients were premedicated with hydroxyzine 2 mg kg^{-1} 90 min before surgery. Atropine was not administered. In the anaesthetic room, before lumbar extradural anaesthesia, a 16-gauge cannula was inserted into a peripheral vein in an antecubital fossa. This cannula was used for fluid preload in all patients, who were allocated randomly to group RL: Ringer's lactate solution 270 mosmol litre^{-1}; group NS: 0.9 isotonic sodium chloride 306 mosmol litre^{-1}; group HS: 5% hypertonic saline 1700 mosmol litre^{-1}. The 5% HS solution was prepared by adding 250 ml of 20% HS to distilled water 150 ml. In all groups, patients received an equal amount of sodium (2 mmol kg^{-1}) (group RL 15 ml kg^{-1}; group NS 13 ml kg^{-1}; group

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HS 2.3 ml kg^{-1}). The time required for fluid preload was noted in each patient. No more fluid was given during the rest of the procedure. Immediately after fluid preload, patients were transferred to the operating theatre and were cared for by a physician (P.V.) blinded to the fluid preload administered previously. Lumbar extradural anaesthesia was performed at the L3–4 interspace with the patient in lateral decubitus position. Lignocaine 2% (6 mg kg^{-1}) with adrenaline 1:240000 was injected in increments of 5 ml every 30 s through a Tuohy needle, an extradural catheter was placed and the patient was repositioned in the supine position. The tourniquet was inflated and the surgical procedure began when the level of the sensory block was satisfactory. Patients breathed oxygen via a face mask and Sp_{O_2} was monitored continuously using a pulse oximeter (Nellcor N 200). Heart rate (HR), systolic, diastolic and mean arterial pressure (MAP) were measured non-invasively before fluid preload (control), after preload and every 2 min during the following 90 min (Dinamap). A 3-mg bolus of ephedrine was administered i.v. during the course of lumbar extradural anaesthesia whenever MAP decreased to less than 80% of its control value. Boluses of midazolam 1 mg were administered as required for sedation. The highest cutaneous level of the sensory block was determined by cold sensation and the patients were questioned concerning side effects. Blood samples were obtained from a venous cannula inserted in the opposite antecubital fossa, before and after fluid preload and 30 and 90 min later. Plasma concentrations of sodium, potassium, chlorine, bicarbonate and proteins, and PCV were measured.

Results are expressed as mean (SD). Statistical analysis included ANOVA followed by an appropriate *post-hoc* test for quantitative data, chi-square analysis with Yates' correction and the Kruskal–Wallis test for non-parametric data. $P < 0.05$ was considered as the minimum level of statistical significance.

RESULTS

Patients were similar in physical characteristics (table I) and initial values of HR and MAP. Volume and duration of fluid preload were significantly less in group HS than in the two other groups (table II). Groups RL and NS were not significantly different for volume and duration of fluid preloading. There was no significant difference between groups in the number of blocked segments and the total amount of ephedrine administered (table I).

Fluid preloading was associated with a significant increase in HR, whereas lumbar extradural anaesthesia induced a significant decrease in MAP and a significant increase in HR (fig. 1). The maximal decrease in MAP was similar in the three groups (RL 23 (13)%; NS 24 (15)%; HS 31 (10)%). Three types of side effects were observed: thirst, headache

TABLE I. *Patient data for the three groups: Ringer lactate solution (RL), isotonic saline NS and 5% hypertonic saline (HS) (mean (range or SD))*

	Sex (M/F)	Age (yr)	Weight (kg)	Height (cm)
RL (n = 10)	4/6	44.3 (29–65)	62.3 (10.1)	165.2 (8.9)
NS (n = 10)	7/3	38.7 (26–60)	71.2 (10.7)	174.2 (8.7)
HS (n = 10)	4/6	34.4 (18–56)	69.7 (10.7)	171.3 (9.5)

TABLE II. *Volume and duration of fluid preloading, number of blocked segments (Blocked) and total amount of ephedrine administered in the three groups: Ringer's lactate solution (RL), isotonic saline (NS) and 5% hypertonic saline (HS).* *$P < 0.05$ *vs RL and NS*

	RL	NS	HS
Volume (ml)	932 (166)	903 (144)	160 (25)*
Duration (min)	21.2 (6.0)	17.7 (3.3)	8.8 (2.9)*
Blocked (No.)	17 (3)	17 (3)	18 (3)
Ephedrine (mg)	12 (20)	13 (15)	9 (9)

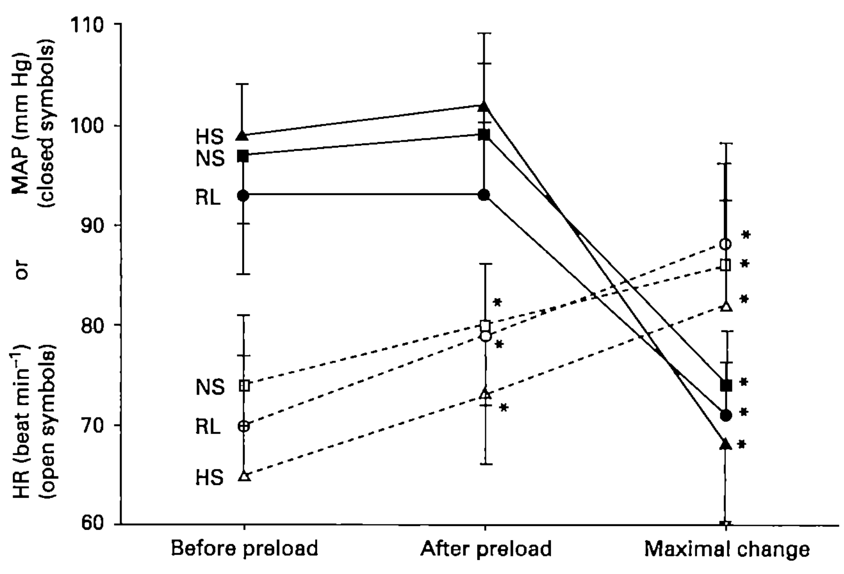

FIG. 1. Changes in heart rate (open symbols) and mean arterial pressure (closed symbols) with each of the three solutes tested: RL = Ringer lactate; NS = isotonic saline; HS = hypertonic saline. *$P < 0.05$ *vs* control value.

TABLE III. *Heart rate (HR) and mean arterial pressure (MAP) before and after fluid loading (FL) in the three groups.* *$P < 0.05$ vs *control value*

	Group RL	Group NS	Group HS
HR (beat min^{-1})			
Before FL	69.4 (14.3)	73.6 (11.6)	64.8 (12.0)
After FL	79.3 (15.7)*	80 (15.15)*	73.1 (13.4)*
MAP (mm Hg)			
Before FL	92.6 (15.8)	97.2 (14.5)	98.9 (9.9)
After FL	92.5 (15.6)	98.5 (16.7)	101.5 (14.3)

and a warm sensation either generally or along the infused vein (table III). The incidence of side effects was not different between groups and the infusion was not painful in any group.

Plasma concentration of sodium did not change significantly in groups RL and NS. In group HS, plasma concentration of sodium increased slightly but significantly after fluid preload (2.2 (1.5) %) and remained significantly increased at 30 and 90 min after the end of preload. The greatest plasma concentration of sodium observed in group HS was 147 mmol $litre^{-1}$. A significant decrease in plasma concentration of protein was observed immediately after fluid preload in the three groups, but this was evident until the end of the study only in the HS group. PCV did not change with fluid preloading in the RL group; in the NS group it decreased, but the change was significant only in the first sample after preload. In the HS group, this decrease was significant until the 90-min sample. Other data are reported in table IV.

DISCUSSION

Our study showed that with RL, NS and HS when the same amount of sodium was infused during fluid preloading, patients required similar amounts of ephedrine after lumbar extradural anaesthesia in order to maintain an adequate arterial pressure. HS 5 % contains 6.5 times more sodium than NS and the same amount of sodium was given 2.5 times faster than with RL or NS, as the volume to infuse was smaller. In this study infusion of HS 2.3 ml kg^{-1} was tolerated well and it produced a mild and transient hypernatraemia.

The osmolality of the extracellular fluids depends mainly on sodium concentration. The osmotic pressure induced by the infusion of HS leads to an almost instantaneous [7] outward movement of intracellular water, which may explain the haemodilution observed immediately after fluid preload. However, the serum protein concentration remained significantly decreased at 30 and 90 min only in the HS group. This implies that, for the same amount of sodium infused, the extracellular fluid expansion is more prolonged after an infusion of HS than after RL or NS solution. However, this result remains to be confirmed. The magnitude of the water transfer can be calculated simply [8]. Although the infusion of 5 % HS 160 ml in an adult produces approximately a 2-litre increase in the extracellular volume, HS-induced haemodynamic changes and their duration cannot be related solely to water movement. HS induces an intense and prolonged venoconstriction [9, 10]. This reflex vascular effect

TABLE IV. *Serum concentrations of electrolytes and protein and PCV before and after, and 30 min and 90 min after the end of fluid preloading (FP) with Ringer's lactate solution (RL), isotonic saline (NS) and 5% hypertonic saline (HS) (mean* SD*) [interquartile range].* *$P < 0.05$; **$P < 0.01$; vs *control value*

	Before FP	After FP	30 min	90 min
Sodium (mmol $litre^{-1}$)				
RL	138.8 (2.4) [136–143]	138.2 (2.8) [134–142]	137.8 (3.2) [132–141]	139 (1.8) [136–141]
NS	140.4 (1.1) [139–142]	140.9 (1.5) [138–143]	139.8 (1.4) [137–142]	140.4 (1.7) [138–142]
HS	140.7 (2.1) [137–143]	143.7 (1.7) [142–147]*	142.4 (2.3) [138–146]*	142.4 (1.9) [140–146]*
Potassium (mmol $litre^{-1}$)				
RL	3.7 (0.3) [3.1–4.2]	3.7 (0.5) [3.0–4.5]	3.8 (0.5) [3.4–4.7]	3.8 (0.7) [3.1–4.8]
NS	3.8 (0.3) [3.5–4.1]	4.0 (0.5) [3.5–4.7]	3.7 (0.2) [3.5–3.9]	3.9 (0.3) [3.6–4.4]
HS	3.8 (0.3) [3.3–4.2]	3.8 (0.4) [3.3–4.3]	3.8 (0.3) [3.3–4.3]	4.0 (0.4) [3.5–4.7]
Chlorine (mmol $litre^{-1}$)				
RL	102.7 (2.3) [99–106]	103.2 (2.9) [100–109]	103.4 (2.7) [100–107]	103.4 (2.9) [100–109]
NS	102.8 (2.2) [99–106]	105.2 (2.0) [101–108]**	104.6 (2.2) [101–108]**	104.9 (2.5) [102–110]**
HS	104.6 (1.4) [103–107]	107.5 (1.8) [105–110]**	107.2 (2.0) [105–112]**	107.1 (2.2) [103–110]*
Bicarbonates (mmol $litre^{-1}$)				
RL	26.8 (1.9) [24–30]	26 (2.5) [23–30]	25.3 (1.8) [23–28]	25.9 (2.5) [24–31]
NS	25.9 (2.8) [21–30]	26 (2.4) [21–29]	24.9 (2.2) [21–28]	25.9 (3.2) [20–31]
HS	25.9 (2.6) [21–29]	26.5 (2.3) [23–30]	25.7 (2.6) [22–30]	26.1 (2.4) [24–29]
Proteins (g $litre^{-1}$)				
RL	72.1 (4.1) [66–78]	66.3 (2.7) [63–71]*	71.8 (5.8) [66–83]	72.3 (8.0) [63–87]
NS	72.2 (3.6) [68–78]	66.7 (3.7) [61–73]*	72.6 (3.7) [68–78]	72.8 (3.1) [68–78]
HS	73.4 (4.2) [64–80]	68.7 (4.1) [61–72]**	69.9 (4.5) [62–78]*	69.0 (3.6) [64–74]*
PCV (%)				
RL	37.8 (5.2) [32.5–47.4]	37.2 (5.7) [30.2–45.3]	39.3 (4.6) [33.6–45.2]	38.9 (5.0) [33.3–45.4]
NS	41.7 (2.6) [38.2–46.6]	39.2 (2.5) [36.9–44.3]**	39.5 (2.7) [35.3–42.5]	39.7 (2.6) [35.6–42.6]
HS	42.4 (3.5) [34.2–45]	39.7 (3.4) [33–42.9]**	41.2 (3.4) [34.1–43.8]**	40.2 (3.4) [33.6–44]**

originates in the lung and is mediated by the vagus nerve [11, 12]. Because our patients were undergoing minor peripheral orthopaedic surgery, it was not possible to measure changes in fluid compartments.

The clinical side effects observed during and after infusion of HS were probably related to the hypertonicity of the solution. However, these side effects were minimal in intensity and duration. In many clinical studies, good tolerance was reported [3, 4, 13–15]. Infusions of 7.5 % HS 2400 mmol $litre^{-1}$ up to 400 ml have been reported to be safe [4]. Hypertonicity *per se* does not necessarily induce phlebitis if the duration of infusion is limited [3]. However it is important to avoid extravasation.

The potential disadvantages of HS administration include hypernatraemia, hyperchloraemia, hyperosmolality and hypokalaemia [16]. In our study, patients who received HS had a significant increase in plasma sodium concentration. However, this increase was minimal and the maximal plasma sodium concentration observed was 147 mmol $litre^{-1}$. Several studies [13–16] have demonstrated absence of side effects of sodium concentrations of 160 mmol $litre^{-1}$. HS 5 % (2.3 ml kg^{-1}) is well tolerated and may be useful when rapid fluid preloading is desired and in situations where excess free water administration is not desired. However, the limits of HS use remain to be defined.

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CRICOID PRESSURE MAY PREVENT INSERTION OF THE LARYNGEAL MASK AIRWAY

J. M. ANSERMINO AND C. E. BLOGG

SUMMARY

We have studied 42 female patients undergoing elective day-case surgery allocated randomly to two groups. After induction of anaesthesia an attempt was made to insert a laryngeal mask airway after application of cricoid pressure in one group or with no cricoid pressure in the other. The anaesthetist was unaware of the application, or not, of cricoid pressure. Successful insertion was achieved at the first or second attempt in 19 of the 22 patients in the non-cricoid pressure group, but in only three of the 20 patients in the cricoid pressure group (χ^2 18.62, P <0.001). The laryngeal mask airway was then inserted successfully in all 17 patients after removal of cricoid pressure. The implications of having to remove cricoid pressure if a laryngeal mask airway is to be inserted are discussed. (Br. J. Anaesth. 1992; **69**: 465–467)

KEY WORDS

Equipment: laryngeal mask airway. Larynx: cricoid pressure.

The laryngeal mask airway (LMA) has proved to be an effective alternative for achieving a clear airway in cases of difficult or impossible tracheal intubation [1]. It has also been used successfully in obstetric anaesthesia in cases of failed intubation [2–4]. However, a major concern is that the LMA does not provide protection against aspiration of gastric contents [5] and is not recommended for use when there is a significant risk of regurgitation and aspiration. Nevertheless, in some circumstances use of the LMA may offer the best hope of achieving a patent airway if conventional tracheal intubation is not possible.

The application of pressure to the cricoid cartilage is used routinely during induction of anaesthesia in any patient who is at risk of aspiration of gastric contents. Backward pressure applied dorsally on the cricoid cartilage occludes the upper oesophagus against the bodies of the cervical vertebrae and prevents regurgitation [6]. It has been recommended, but without any evidence, that cricoid pressure be maintained during insertion of the LMA in the event of a failed intubation [7].

The purpose of the study was to assess the effect of the application of cricoid pressure on the ability to insert the LMA correctly in a group of female patients of child bearing age.

PATIENTS AND METHODS

We studied 42 female patients, ASA I or II, aged 18–40 yr, undergoing elective day-case gynaecological or breast surgery for which use of a LMA was appropriate. All gave informed consent to this single-blind, randomized, controlled study which was approved by the local Ethics Committee.

All patients received premedication comprising oral ranitidine 150 mg and metoclopramide 10 mg. An appropriate i.v. cannula was inserted for administration of drugs and fluid. Monitoring (display of ECG, non-invasive measurement of arterial pressure and pulse oximetry) was begun before induction of anaesthesia with a combination of fentanyl 1.5 $\mu g\ kg^{-1}$ and propofol 2–3 $mg\ kg^{-1}$. Ten breaths of oxygen and 2% isoflurane were administered by manual ventilation of the lungs with a bag and face mask system to confirm adequate depth of anaesthesia and to ensure oxygenation. Neuromuscular blocking drugs were not used. The patient's head was positioned with the neck slightly flexed and the head extended. An experienced assistant simultaneously placed a screen to obscure the anterior aspect of the neck and chest from one of the authors who was to insert the LMA. The screen consisted of a large green drape suspended from two infusion stands placed on each side of the patient. The screen extended from above the investigator's head height, sloped slightly towards the head of the patient and passed just under the chin before being tucked under the head on each side.

The patients were allocated randomly to have either two-handed cricoid pressure [8], applied by the assistant in the usual way, or to have the assistant's hands placed in position but no cricoid pressure applied. An attempt was then made to insert a size 3 LMA according to the manufacturer's recommendations [9]. After insertion, the cuff was inflated with 30 ml of air. The successful placement of the LMA was taken to be the presence of all of the following: resistance to continued advancement, outward movement of the LMA from the mouth on inflation of the cuff, appearance of condensation in the LMA tubing after attachment to the anaesthetic

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system and gentle manual ventilation with satisfactory compliance. Chest wall movement was not assessed visually because of the presence of the screen. The number of attempts and time taken for successful insertion were recorded.

If insertion proved not to be possible after the second attempt, the screen was removed and the assistant stopped applying or mimicking cricoid pressure. Anaesthesia was deepened with administration of i.v. propofol if required, and another attempt at insertion was made.

The data were analysed using the unpaired Student's t test to compare age and weight, while chi-square analyses were used to compare successful insertion in the two groups.

RESULTS

Forty-two patients were studied. The ages and weights of the two groups were similar (table I). Cricoid pressure was not applied in 22 patients, in whom the LMA was inserted successfully on the first attempt in 16 patients. A second attempt was required in three. In the remaining three patients, the LMA was inserted successfully only after the removal of the screen. Two of these patients had developed laryngospasm and required additional i.v. propofol before the LMA was easily inserted. The remaining patient required the use of a laryngoscope to insert the LMA (fig. 1).

The LMA was inserted successfully at the first attempt in only two of the 20 patients in whom cricoid pressure was applied. (One successful insertion was achieved on the second attempt.) This was significantly different from the patients in whom cricoid pressure was not applied (χ^2 18.62; $P < 0.001$). However, after removal of both the screen and cricoid pressure, the LMA was inserted at the first attempt in all 17 of the remaining patients. The time for insertion and the adequacy of the seal could not be compared statistically because of the small number of successful insertions in the cricoid pressure group.

TABLE I. *Patient data (mean (range or* SD*))*

	n	Age (yr)	Weight (kg)
Cricoid pressure	20	34.4 (27–40)	64.3 (1.30)
No cricoid pressure	22	33.7 (25–40)	61.5 (1.63)

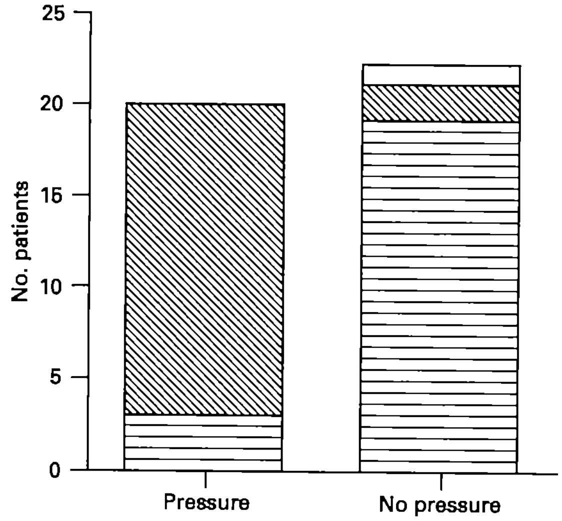

FIG. 1. Success and failure of insertion of laryngeal mask airway in patients with and without cricoid pressure. ☐ = Failure; ▨ = achieved after removal of screen; ⊟ = achieved at first or second attempt.

DISCUSSION

There are no studies to date on the effect of the LMA on the competence of the upper oesophageal sphincter and the effectiveness of cricoid pressure after insertion of the LMA. When positioned correctly, the elliptical cuff of the LMA projects downwards into the hypopharynx below the level of the cricoid cartilage. If cricoid pressure is maintained during insertion of the LMA, it would seem possible that cricoid pressure could prevent correct placement of the LMA. We did not investigate the effectiveness of cricoid pressure subsequent to insertion of the LMA.

It is difficult to standardize the force required for effective cricoid pressure. Although a yoke was designed (similar to that described previously [10]) for this study in order to apply a standard pressure to the cricoid, the device proved to have too much lateral instability. Thus, to reproduce the clinical situation, cricoid pressure was applied in a standard manner by an experienced assistant.

Three assistants were used during the course of the study, but only one assistant at any time. They were given careful instructions and ample time to identify the cricoid cartilage and apply a firm two-handed cricoid pressure.

The number of unsuccessful insertions in the group without cricoid pressure applied is perhaps greater than that reported in routine practice when a prototype was used [11]. However, because observation of chest movement was prevented by the screen and strict criteria were used for successful insertion of the LMA, reduced success was anticipated.

Others have studied the effects of cricoid pressure on the correct positioning of the laryngeal mask airway [12, 13], with contrasting success. Heath and Allagain [12], in an unblinded consecutive study of patients with normal anatomy, failed to place a tracheal tube through an LMA in 22 of 50 patients without releasing cricoid pressure. Those patients had also received neuromuscular blocking agents. It was suggested that the cricoid pressure should be released momentarily during placement of the LMA and again during insertion of the tracheal tube. This was accepted as a compromise between protection against regurgitation and rapid, successful intubation. In contrast, in the correspondence which followed, Brimacombe [13] suggested from the results of another unblinded, consecutive study that application of cricoid pressure did not significantly reduce the ease of insertion of the LMA; nevertheless, he found that the oesophagus was seen in four of 40 patients who had prior cricoid pressure applied and in three of 40 who did not. The increased difficulty in placing a tracheal tube [12] with cricoid pressure can be explained by the increased anterior tilt of the laryngeal aperture of between 10° and 40° in every patient [13]. Our findings of a success rate of only three in 20 patients for correct insertion of an LMA at first attempt without release of cricoid pressure may be explained by the use of very stringent criteria for accurate placement, applied by an observer blinded to both the application of cricoid pressure and chest movement, in patients who had not been given neuromuscular blocking drugs. Both investigators in the present study have had considerable experience of insertion of the LMA (one (C.E.B.) having achieved 648 successful insertions in 10 months) and lack of skill in insertion of the LMA is thus unlikely to have been a factor in the low success rate whilst cricoid pressure was applied.

The precise role of the LMA in the failed intubation drill requires elucidation. The major disadvantage of the LMA is that it does not reliably protect against aspiration of gastric contents. The potential benefit of maintaining a patent airway with the LMA needs to be weighed against a potentially increased risk of aspiration and the possibility that it may even direct regurgitated material towards the larynx [14]. Further, prolonged failure to intubate the trachea after repeated attempts may allow sufficient time for the effect of the induction agent and shorter-acting neuromuscular blocking drugs to abate. Inability to deepen inhalation anaesthesia during this period may result in a lightly anaesthetized patient in whom the insertion of a LMA could promote vomiting or laryngospasm.

Our data suggest that, in the event of a failed intubation, in a patient in whom there is a significant risk of regurgitation and for whom ventilation can be maintained with a face mask whilst cricoid pressure is applied, it would be safer to continue with face mask anaesthesia rather than try to insert an LMA. If maintenance of a clear airway is impossible, the insertion of the LMA may be an alternative to cricothyroid puncture. Cricothyrotomy or insertion of a LMA each require transient removal of cricoid pressure, thus increasing the risk of aspiration. However, the consequences of aspiration are likely to be treatable and are preferred to the inevitable fatal progression to anoxia. The transient release of cricoid pressure to facilitate insertion of the LMA may carry only a small increased risk, but the effect of the LMA on the integrity of the upper oesophageal sphincter and on the efficacy of cricoid pressure after correct placement of the LMA is not known.

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IS THE "K-TYPE" CAFFEINE–HALOTHANE RESPONDER SUSCEPTIBLE TO MALIGNANT HYPERTHERMIA?

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SUMMARY

The "K-type" designation is used to describe a patient being investigated for malignant hyperthermia (MH) when concurrent administration of caffeine and halothane induces muscle contracture (rigidity, spasm) in vitro, *but when halothane and caffeine given separately produce a normal response. It is accepted in some centres that K-type individuals are susceptible to malignant hyperthermia (MHS). In this paper, the K-type is shown not to correlate with the MH susceptible (MHS) status as accepted by the European MH group.* (Br. J. Anaesth. 1992; **69**: 468–470)

KEY WORDS

Hyperthermia: malignant

Ideally, a screening test should distinguish clearly between two groups of patients, normal and abnormal, without any overlap. The value of the test diminishes as the amount of overlap between the two groups increases. Unfortunately, this simple rule, pointed out by Ording [1], has not been applied in all the tests for malignant hyperthermia (MH) which have been described and this has led to confusion, even in the interpretation of the *in vitro* living muscle contracture test (IVCT) results performed for MH screening in various centres.

Since IVCT for the diagnosis of MH susceptibility (MHS) first began in 1970–71 [2, 3], there has been controversy about the value of the combined caffeine–halothane contracture test (CHCT) in which caffeine and halothane are administered concurrently [4]. It has been claimed that, when the CHCT gives a positive result when the halothane and caffeine tests (separately) are negative, this identifies a group of patients susceptible to MH, designated by the "K-type" response [1, 5, 6]. At the present time, the European MH Group [7] does not accept that the CHCT indicates MH susceptibility, and therefore rejects the K-type as a potential clinical entity, the main reason for this rejection being the anecdotal recognition that K-types are found in 10–30 % of the general population. The comparative rarity of MHS axiomatically should militate against an association between K-type and MHS.

More recently, the North American MH Registry has published a procedure which differs from the European procedure mainly in the concentrations of halothane used. However, it still allows the use of the CHCT as an optional test until it can be further evaluated [8]. This paper reports such an evaluation.

PATIENTS AND METHODS

We studied all patients attending for routine MH screening using the European procedure. Patients were investigated in the usual way [9]. This involves the exposure of four living muscle strips (each weighing about 80 mg) taken from the vastus medialis muscle, to incremental doses of halothane (0.5, 1.0 and 2.0 %) and caffeine (0.5, 1.0, 1.5, 2.0 mmol litre^{-1}) separately in a 2-ml tissue bath which has been designed specifically for this purpose. The muscle is stimulated electrically at 0.2 Hz and the bath is perfused continuously with Kreb's solution at 37 °C. The patient is regarded as MHS (susceptible) if the muscle produces a sustained increase in baseline tension (contracture) of 0.2 g to both halothane (2 % or less) and caffeine (2 mmol litre^{-1} or less) on separate specimens. If the muscle produces an abnormal response to only one agent, the patient is classified as MHE (equivocal). If both tests are normal, the patient is regarded as MHN (normal).

In addition to the two halothane tests (static and dynamic) and the two caffeine tests (static), we exposed a fifth muscle specimen to combined halothane and caffeine using the method described by Larach [10], except that the specimen was exposed to halothane for 3 min, not 10 min. (Current quality control measurements of the halothane concentrations in the tissue bath in our laboratory show that equilibration is achieved within 1 min, allowing us to reduce the time of exposure to halothane from 10 min to 3 min. The rapid equilibration results from the small size of our tissue bath (2 ml) compared with most other tissue baths in use (50–100 ml).) The CHCT was regarded as positive if the subsequent addition of caffeine 1.0 mmol litre^{-1} or less resulted in a further increase in tension of greater than 1.0 g.

The results of the CHCT were compared with the results obtained with the European MH Group

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TABLE I. *Classification of patients screened for MH: European MH Group procedure compared with CHCT. Chi-square analysis of the CHCT (K-type) results for the MHS and MHN patients: significant difference* ($P < 0.001$)

European classification	Total	K-type	K-type in each category (%)
MHN	67	8	12
MHS	22	12	55
MHE(h)	12	6	50
MHE(c)	0	—	—
MHS + MHE(h)	34	18	53
Total no. patients	101		

procedure. When all tests were normal the patient was classified as MHN. When muscle contractures of greater than 0.2 g were obtained with both halothane and caffeine administered separately to different specimens of muscle, classification was as MHS. MHE identified those patients in whom only one group of tests was abnormal; MHE(h) identified an abnormal halothane test and MHE(c) an abnormal caffeine test.

RESULTS

One hundred and one patients were included in the present study (table I). Twelve per cent of MHN patients had a positive CHCT only and thus were classified as K-types. Conversely, only 55 % of the MHS patients had a positive CHCT result, a similar result (50 %) being obtained for the MHE(h) group. Overall, the incidence of a K-type CHCT response was 28 %. χ^2 analysis of the data, however, indicated a significant difference between the MHS and MHN groups based on the results of the CHCT ($P < 0.001$).

None of the eight K-types in the MHN group had caused any clinical concern. One patient was the sibling of a proband who died during anaesthesia many years ago (the family has not yet been confirmed as MHS); one patient was the sibling of a non-anaesthetic proband investigated elsewhere; two patients were relatives of confirmed MHS patients. There were also four probands, none of whom had experienced fulminant or moderately severe anaesthetic MH reactions [11]. Briefly, their reactions were as follows: (1) an intraoperative pyrexia and tachycardia shortly after induction, causing sweating and flushing, which resolved spontaneously on withdrawal of the anaesthetic agents; (2) an intraoperative pyrexia of 38.7 °C increasing to 40.2 °C after operation; (3) an undocumented severe postoperative pyrexia many years ago; (4) a history of masseter spasm lasting 20 min with increased serum creatine kinase concentration.

DISCUSSION

The use of the European MH Group procedure has been validated by the pooling of results from many European centres. This showed that no clinically fulminant case of MH was classified as MHN and that, of the controls, two patients (3 %) were just within the abnormal range for one but not both agents—one was MHE for halothane and one was MHE for caffeine. Thus the thresholds (reflecting the confidence limits) of the European procedure are already set to allow for a small number of false positives for safety [unpublished data presented at European MH Group meeting in Munich, 1990]. Any further difference obtained by another test increases the number of false positives or negatives to more than those accepted by the procedure.

An incidence of 12 % K-type individuals in the MHN group accords with other reports (verbal and unsubstantiated) that between 10–30 % of controls are K-type. This leads some to argue the case for a different type of inheritance pattern in MH [5], but recent genetic studies do not confirm a more complex inheritance [12–14].

It is difficult to explain why only 50 % of the MHS patients were positive to the CHCT when a clear correlation between the two tests might have been expected. This could be a result of the method of interpreting the result. In some patients (all of those whose halothane thresholds occurred at 0.5 % and 1.0 %) the initial exposure to 1 % halothane produced a contracture well in excess of the threshold values for the European static halothane test, but the subsequent addition of caffeine did not produce a further contracture greater than 1.0 g. It is questionable if the CHCT should be classed as negative in this situation.

Despite the statistical evidence to support the use of the CHCT, the test does lack specificity, being unable to identify with adequate separation the two groups of patients. As the CHCT can produce both false positive and false negative results, this renders the designation K-type meaningless as far as MH screening is concerned and is potentially dangerous. We believe it should no longer be used in relation to MH phenotyping.

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British Journal of Anaesthesia 1992; **69**: 471–473

EVALUATION OF SPIN RESONANCE SPECTROSCOPY OF RED BLOOD CELL MEMBRANES TO DETECT MALIGNANT HYPERTHERMIA SUSCEPTIBILITY

P. J. HALSALL, F. R. ELLIS AND P. F. KNOWLES

SUMMARY

We have evaluated a spin labelled electron spin resonance technique to identify malignant hyperthermia susceptible (MHS) patients. We studied 19 patients, 10 MHS and nine MHN (normal), using the standard European procedure. We were unable to obtain any evidence that this technique could be used to diagnose MH susceptibility. Furthermore, there was no significant difference in the fluidity of the red blood cell membranes between the two groups, which would have been indicative of a generalized membrane abnormality in MH. (Br. J. Anaesth. 1992; **69**: 471–473)

KEY WORDS

Hyperthermia: malignant. Measurement techniques: electron spin resonance.

Although the exact aetiology of malignant hyperthermia (MH) is uncertain, it is known to be a membrane disorder involving both the sarcolemma [1] and the sarcoplasmic reticulum (SR) [2]; thus abnormality of the excitation–contraction coupling mechanism is most likely [3]. There is evidence to suggest that calcium homeostasis is impaired in MH patients when exposed to the triggering agents [4]. A current view is that MH is caused by an abnormality of calcium control, possibly involving the ryanodine receptor, which lies within the SR but is attached to the dihydropyridine calcium channel in the T tubule [5]. Tissues other than muscle have been implicated in MH, including white blood cells (WBC) [6] and red blood cells (RBC) [7]; on the basis of these reports, MH may be considered a generalized membrane disorder.

Using spin labelling of RBC and studying electron spin resonance (ESR) spectroscopy, Ohnishi and coworkers [8] described a method which apparently distinguished, without overlap, two groups of patients who were MH susceptible (MHS) and MH normal (MHN). They claimed to predict successfully the muscle biopsy result in 13 of 14 patients (seven MHS and six MHN). This study not only suggested a basis for an alternative test for MH which would be less invasive for the patient, but also confirmed the suggestion that the membrane defect in muscle might be expressed in other plasma membranes, such as in the RBC.

This potentially important finding needed to be substantiated and the present paper describes our observations and conclusions.

PATIENTS AND METHODS

Patients presenting for muscle biopsy screening for MH were asked to donate 10 ml of venous blood, taken at the same time as routine samples for measurement of creatine kinase (CK). The blood was stored in citrate–phosphate–dextrose (CPD) at 4 °C for about 48 h until processed according to the method described by Ohnishi and colleagues [8]. The blood was first filtered though a cotton column to remove all WBC. The remaining RBC sample was washed twice in a buffered solution containing the following (mmol litre^{-1}): NaCl 108, KCl 5, $MgCl_2$ 1.2, $NaHCO_3$ 24, NaH_2PO_4 2.4, glucose 30, adenine 1, inosine 1 and 0.1 % bovine serum albumin (BSA). Then the spin label 16-deoxylstearic acid (16DS) was added to the washed RBC (12 μg ml^{-1}) with ATP 1 mmol litre^{-1} to a PCV of 20 %, and incubated at 4 °C overnight. After two additional wash-centrifugations using the first buffer minus BSA to remove the excess spin label, ATP 1 mmol litre^{-1}, CaCl 3 mmol litre^{-1} and 0.05 % BSA were added to give a final PCV of 30 %. The sample was then divided into two. To the first sample, halothane (as a solution in dimethyl sulphoxide (DMSO) of concentration 141 mmol litre^{-1}) was added to produce a final halothane concentration of 3 mmol litre^{-1}, whilst the second (control) sample had only DMSO 141 mmol litre^{-1} added. Halothane 3 mmol litre^{-1} was chosen because this was the concentration found by Ohnishi and colleagues to distinguish most clearly between MHS and MHN patients [8]. The samples were then placed in capillary tubes, sealed at both ends, centrifuged (1500 *g*) to compact the labelled RBC and stored on ice before ESR measurements (completed within 2–3 h).

The ESR measurements were made at 37 °C using a Bruker ER-200 9GHZ spectrometer equipped

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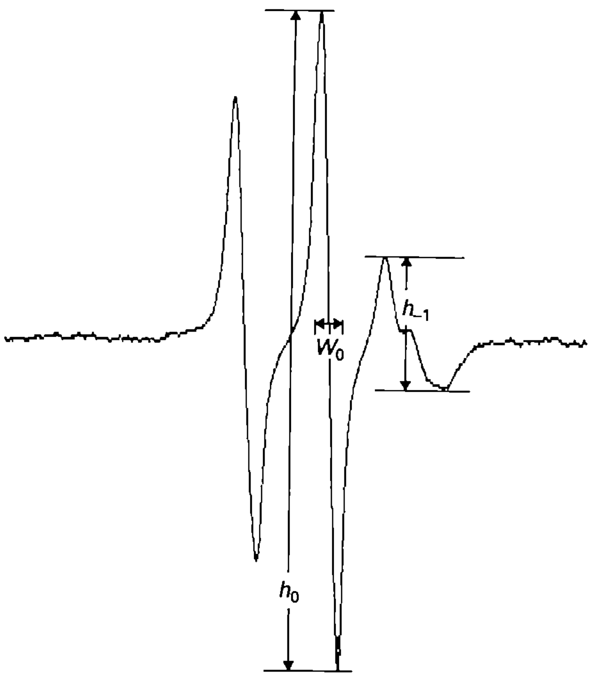

FIG. 1. Typical spectrum (average of five scans).

with nitrogen gas flow temperature control to 0.5 °C. The spectrometer was interfaced to an Acorn 1770 DFS microcomputer with Microlink interface (Biodata, Manchester, U.K.) via an IEEE-488 bus. It was found that very small changes in the value of the central line width (W_0) gave large changes in the final correlation time, therefore the spectra were enlarged by a factor of two to increase the accuracy of the measurement (using set square and calipers) of the peak heights and widths. The correlation time ("tumbling" time, T_c) was calculated using the formula [9]:

$$T_c = (6.5\times10^{-10})\,W_0\,[(h_0/h_{-1})^{1/2}-1]$$

where W_0 = peak-to-peak line heights in the midfield line; h_0 and h_{-1} = peak-to-peak line heights in the midfield and high field regions of the spectrum, respectively (fig. 1). Muscle biopsy screening was performed according to the European MH Group procedure [10, 11] and only patients who were classified as MHS and MHN were included in the study. At the time of the ESR measurements, the MH status of the patient was unknown. Altogether, 19 patients were included in the study: 10 MHS and nine MHN.

RESULTS

The changes in correlation time produced by the addition of halothane are shown in table I and figure 2; a decrease in correlation time indicates an increase in membrane fluidity. The changes in correlation time given are the control values minus the values in the presence of halothane; thus if the correlation time decreased after addition of halothane, the change in T_c would be positive, and *vice versa*. Applying the *t* test to both the control values and the changes caused by halothane between the MHS and MHN patients showed no significant difference ($P < 0.5$ and < 0.2, respectively). Although there was no significant effect on the control values by halothane, there was an apparent alteration in the distribution of the correlation times after exposure to halothane, indicated by increase in correlation time (decreased fluidity) for the MHN patients, compared with no obvious change for the MHS patients (fig. 2) (ns, Mann–Whitney).

There was a large amount of overlap between the results for the MHS and the MHN groups.

Figure 2 also compares our results with those of Ohnishi's group [8]. It can be seen that the changes in correlation time reported by Ohnishi and colleagues are an order of magnitude smaller than our values.

TABLE I. *Correlation times ($\times 10^{-10}$ s) for spin labelled RBC from MHS and MHN patients*

MHS			MHN		
Control	Halothane	Change	Control	Halothane	Change
35.51	30.99	4.52	34.16	36.10	−1.94
37.57	37.79	−0.25	34.57	39.52	−4.59
40.11	39.54	0.59	37.67	38.89	−1.22
33.59	40.26	−6.67	37.39	37.79	−0.40
37.75	38.52	−0.77	40.84	40.64	0.20
39.02	35.31	3.71	32.94	40.24	−7.30
40.53	34.10	6.43	37.88	41.25	−3.37
36.94	37.76	−0.82	35.48	30.80	4.68
37.48	34.67	2.76	36.86	36.24	0.62
33.71	35.77	−2.06			

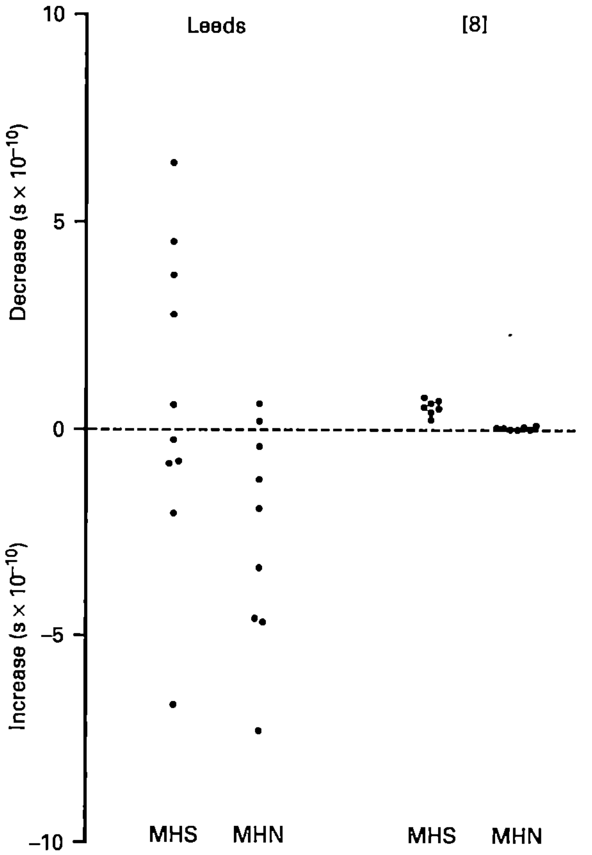

FIG. 2. Changes in correlation time produced by halothane: control values minus values in the presence of halothane (for further explanation, see text). Results from Leeds study compared with those from the study by Ohnishi and colleagues [8].

DISCUSSION

On the basis of our results, we are unable to give a value for the change in correlation time which would distinguish MHN from MHS patients, there being too much overlap between the two groups. In addition, there was no evidence to suggest that halothane had any effect on the mobility of RBC membranes, as there was no significant change in correlation time. These conclusions are contrary to those reached by Ohnishi and colleagues [8], who reported that monitoring of RBC mobility allowed diagnosis of MHS.

Our calculated correlation times are all in the range 3×10^{-9}–4×10^{-9} s and are similar in magnitude to those reported by Ohnishi and colleagues (1.65×10^{-9}–1.75×10^{-9} s) [8]. There is no major disagreement between our findings and those of Ohnishi's group on this point, and similar correlation times with stearic acid spin labels have been reported in the literature [9]. It is in the magnitude of the change in correlation time induced by halothane 3 mmol litre^{-1} in erythrocytes from MHN *vs* MHS subjects that our results differ from those of Ohnishi and colleagues. They found that, for MHN patients, the change was $0.2 \pm 0.5 \times 10^{-11}$ s, whilst for susceptible patients it was $5.5 \pm 1.5 \times 10^{-11}$ s. We have no explanation for the changes in correlation reported by Ohnishi and co-workers being an order of magnitude smaller than ours. Our results are in agreement with those of Cooper and Meddings [12], who have used fluorescence probes to monitor RBC fluidity.

In addition, we have been unable to detect any difference in the membrane fluidity of RBC from MHN and MHS individuals. This argues against a generalized membrane defect in MH. Thatte and co-workers [13] reported that erythrocytes from MHS swine have an altered temperature dependence in both Mg-ATPase activity and membrane fluidity as monitored by the 16DS probe, which suggested a generalized membrane defect in MH. However, a more recent report from the same laboratory [14] found no difference between MHN and MHS swine in the fluidity of skeletal muscle sarcolemma, heavy sarcoplasmic reticulum and transverse tubules, and it was concluded that generalized membrane defects do not appear to be the cause of the defects exhibited by MHS muscle. The findings of Cooper and Meddings [12] support this view.

The major conclusion of this study is that we have been unable to substantiate the findings of Ohnishi and co-workers [8] in relation to providing an alternative non-invasive test for MH. Based on the criteria of Ohnishi's group, 50% of our undoubtedly MHS patients would be classified as normal according to the spin label studies we have performed.

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British Journal of Anaesthesia 1992; **69**: 474–477

FRACTIONAL DELIVERY OF FRESH GAS: A NEW INDEX OF THE EFFICIENCY OF SEMI-CLOSED BREATHING SYSTEMS

P. C. W. BEATTY, G. MEAKIN AND T. E. J. HEALY

SUMMARY

*In earlier clinical studies, we have found a significant difference in the fractional utilization of fresh gas (*F*U) when using an enclosed afferent reservoir breathing system (EAR) for adult patients compared with children. This difference was explained by a large arterial to end-tidal carbon dioxide difference in the adults, reflecting a larger alveolar deadspace. In the present study, a new index of breathing system efficiency, fractional delivery of fresh gas (*F*d) is proposed, which is independent of alveolar deadspace. In order to demonstrate this, values of *F*d were calculated for the EAR during controlled ventilation of adults, children and a lung model. There were no significant differences between the groups. A maximum efficiency of 0.94 for the EAR was close to the theoretical limit of 1.0 predicted by the results at minute volume ventilation to fresh gas flow ratio ($\dot{V}E:\dot{V}F$) values greater than 2.0. For adult patients, the values of *F*d were shown to be significantly greater than the values of *F*U at the same $\dot{V}E:\dot{V}F$ ratio (*F*d = 0.91, *F*U = 0.72 at $\dot{V}E:\dot{V}F = 2.0$ ($P < 0.05$)).* (Br. J. Anaesth. 1992; **69**: 474–477)

KEY WORDS

Equipment: semi-closed breathing systems. Measurement techniques: capnography, fractional fresh gas delivery.

There has been renewed interest in recent years in defining the efficiency of semi-closed anaesthetic breathing systems [1–3]. Much of this interest has centred on the development of enclosed afferent reservoir breathing systems (EAR) and preferential flow systems [4–8], and various methods of defining the efficiency of usage of fresh gas flow have been discussed.

In earlier studies of the Ohmeda enclosed afferent reservoir breathing system (EAR), we used an index termed fractional utilization of fresh gas (*F*U) to measure the efficiency of the system [8, 9]. This index was derived from the alveolar gas equation and calculated as follows:

$$FU = \frac{\dot{V}CO_2}{\dot{V}F \times Fa_{CO_2}} \qquad (1)$$

where $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}F$ = fresh gas flow; Fa_{CO_2} = gas phase concentration with which arterial blood is in equilibrium.

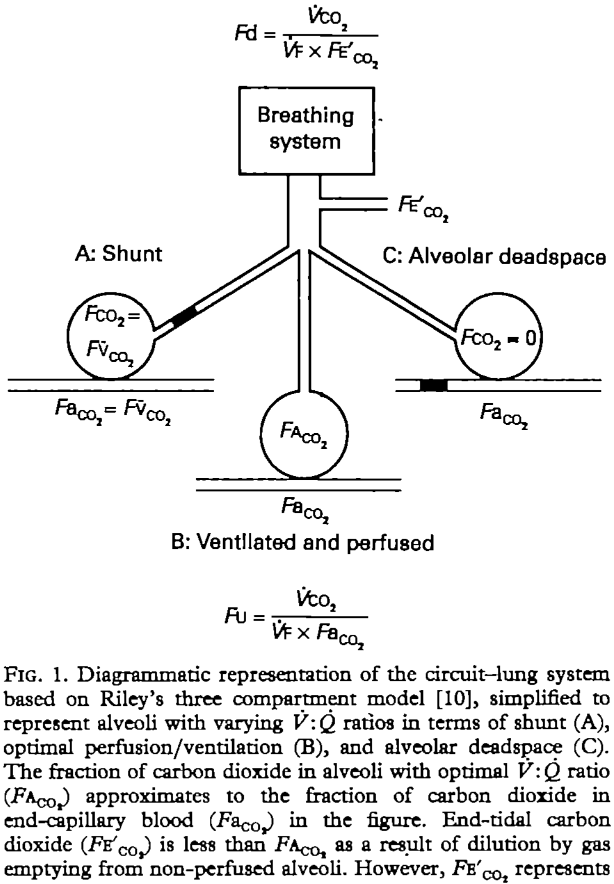
$Fd = \frac{\dot{V}CO_2}{\dot{V}F \times FE'_{CO_2}}$
Breathing system
FE'_{CO_2}
A: Shunt
C: Alveolar deadspace
$FCO_2 = F\bar{V}_{CO_2}$
$FCO_2 = 0$
$Fa_{CO_2} = F\bar{V}_{CO_2}$
FA_{CO_2}
Fa_{CO_2}
Fa_{CO_2}
B: Ventilated and perfused
$FU = \frac{\dot{V}CO_2}{\dot{V}F \times Fa_{CO_2}}$

FIG. 1. Diagrammatic representation of the circuit–lung system based on Riley's three compartment model [10], simplified to represent alveoli with varying $\dot{V}:\dot{Q}$ ratios in terms of shunt (A), optimal perfusion/ventilation (B), and alveolar deadspace (C). The fraction of carbon dioxide in alveoli with optimal $\dot{V}:\dot{Q}$ ratio (FA_{CO_2}) approximates to the fraction of carbon dioxide in end-capillary blood (Fa_{CO_2}) in the figure. End-tidal carbon dioxide (FE'_{CO_2}) is less than FA_{CO_2} as a result of dilution by gas emptying from non-perfused alveoli. However, FE'_{CO_2} represents the mean carbon dioxide concentration of the total alveolar compartment. Alveoli involved in shunt do not contribute to alveolar carbon dioxide content levels and hence do not affect *F*d. *F*U and *F*d represent fractional utilization and fractional delivery of fresh gas calculated from arterial and end-tidal carbon dioxide samples, respectively. It is evident that *F*U measures the efficiency of the breathing system combined with that of the patient's lungs in terms of gas exchange in perfused alveoli. In contrast, *F*d measures efficiency of the breathing system in terms of gas delivered to ventilated alveoli. In the absence of $\dot{V}:\dot{Q}$ mismatch, *F*U and *F*d would be identical. However, in the presence of mismatch, *F*U underestimates the efficiency of the breathing system since it is affected by the efficiency of the patient's lungs. The presence of a shunt (type A alveoli) does not affect this conclusion, because these alveoli are not available for gas exchange or ventilation and will be in equilibrium with mixed venous blood at $F\bar{V}_{CO_2}$.

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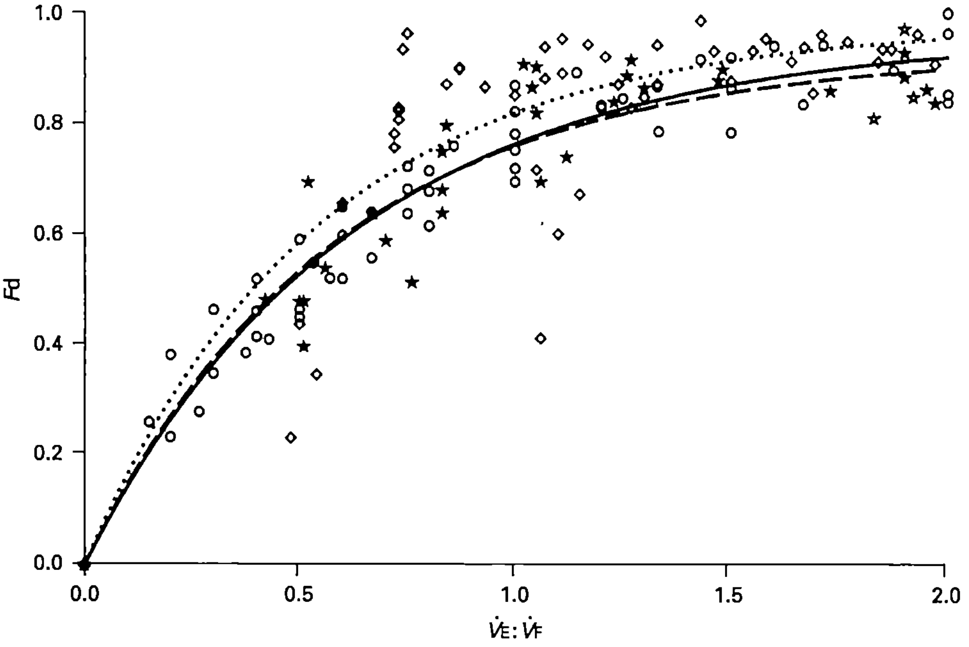

FIG. 2. Fd *vs* $\dot{V}$E: $\dot{V}$F ratio for adult (... ◇ ...), paediatric (—★—) and laboratory data (—○—) under controlled ventilation with best fit lines of the form $y = A(1-e^{-xB})$.

In equation (1), the Fa_{CO_2} approximates to that found in perfused alveoli, and *F*U describes the efficiency of a breathing system in terms of the proportion of $\dot{V}$F which actually takes part in gas exchange [8, 9]. However, if appreciable parts of the lung are ventilated but not perfused, the apparent efficiency of the breathing system is reduced (fig. 1). Such a reduction in *F*U, which can be attributed to the increase in alveolar deadspace, has been observed in elderly patients whose lungs were ventilated with the EAR [8] and is clearly a problem when comparing the efficiencies of different breathing systems.

A possible solution to this problem may be to substitute end-tidal for arterial carbon dioxide concentration in equation (1). This gives a new index of efficiency which we have termed "fractional delivery" (*F*d) given by:

$$Fd = \frac{\dot{V}CO_2}{\dot{V}F \times FE'_{CO_2}} \qquad (2)$$

where FE'_{CO_2} is the end-tidal carbon dioxide concentration.

As FE'_{CO_2} approximates to the mean carbon dioxide concentration of the ventilated alveoli, *F*d should be a measure of the proportion of fresh gas which enters the alveolar compartment, whether or not it takes part in gas exchange. Increasing shunt does not affect the estimate of FA_{CO_2} from FE'_{CO_2} [11]. *F*d values should be similar to those obtained using lung models which have no alveolar deadspace and be independent of patient age.

In order to test this hypothesis, we have calculated *F*d for the EAR in anaesthetized adults, anaesthetized children and a lung model, using equation (2). *F*d has also been compared with values of *F*U obtained clinically.

PATIENTS AND METHODS

The data and methods used in these studies have already been described in detail [8, 9, 12] and are summarized below.

Adult controlled ventilation

Eighteen patients (ASA I–III; mean age 69 yr) were studied using the anaesthetic technique reported [8] with 66% nitrous oxide and 1–2% isoflurane in oxygen. Carbon dioxide evolution was calculated from measurements of the mixed effluent carbon dioxide concentration over a period of 2–5 min, made using a mixing box, dry gas meter and a mass spectrometer (Ohmeda MGM 6000, 80% rise time t_{80} = 100 ms). The flowmeters of the anaesthetic machine were calibrated to provide accurate values of fresh gas flow ($\dot{V}$F). End-tidal carbon dioxide concentration was measured at the catheter mount using the mass spectrometer calibrated against a standard gas mixture (Datex 5.0 ±0.3% carbon dioxide in oxygen). Lungs were ventilated using an Ohmeda 7800 ventilator with an I:E ratio of 1:2 via a cuffed tracheal tube. *F*d was plotted against minute volume ventilation to fresh gas flow ratio ($\dot{V}$E: $\dot{V}$F) as $\dot{V}$F was adjusted to produce a range of $\dot{V}$E: $\dot{V}$F ratios of 0.4–2.5.

Paediatric controlled ventilation

We studied 12 patients (ASA I–II, aged 1–16 yr) using the anaesthetic technique reported [9] including 66% nitrous oxide and 0.5–1.0% isoflurane in oxygen. Measurements of carbon dioxide production were made in a manner similar to that used in the adult controlled ventilation study over periods of 1 min using a mixing box and an infra-red carbon dioxide analyser (Datex Cardiocap II, 80% rise time

t_{80} = 400 ms). A similar analyser, calibrated against a standard gas mixer, was used to measure end-tidal carbon dioxide concentration at the connector end of the tracheal tube. An uncuffed tracheal tube was used and the throat was packed with ribbon gauze to prevent leaks. Tidal volume was maintained at 120 ml kg^{-1} and $\dot{V}_F$ was varied between 1.4 and 5.5 litre, producing a range of $\dot{V}_E:\dot{V}_F$ ratios between 0.6 and 2.9. Maximum ventilatory frequency was 26 b.p.m.

Laboratory experiments

The Ohmeda EAR was connected to a model lung which consisted of a clear plastic box containing an impermeable plastic bag and a multi-branched glass pipe. Carbon dioxide flowed into this bag via the pipe at a rate of 180 ml min^{-1} from a calibrated flowmeter (Gap meter). A Manley test lung was connected to the outside of the box to provide elastic recoil. Carbon dioxide concentration was sampled from the end of the Y-piece of the EAR by the mass spectrometer (Ohmeda MGM 6000). The system was ventilated using an Ohmeda 7800 ventilator, and the effect of varying $\dot{V}_F$ and $\dot{V}_E$ on end-tidal carbon dioxide concentration using a range of $\dot{V}_E:\dot{V}_F$ ratios between 0.1 and 5.0 was recorded with an I:E ratio of 1:2.

RESULTS

The *F*d values and the $\dot{V}_E:\dot{V}_F$ ratios for all three sets of data are shown in figure 2. A curve of the form

$$Fd = A(1 - e^{-B\dot{V}_E:\dot{V}_F})$$

selected arbitrarily was fitted to all three sets of data (Figure Perfect). Interpolated *F*d values at various key $\dot{V}_E:\dot{V}_F$ with their 95% confidence limits are shown in table I. There were no significant differences between the *F*d values.

TABLE I. *Interpolated* Fd *and* Fu for $\dot{V}_E:\dot{V}_F$ *ratios of 0.5, 1.0 and 2.0 (±95% confidence limits of the estimates stated)*

	$\dot{V}_E:\dot{V}_F$		
	0.5	1.0	2.0
Adult data			
*F*d	0.53 (±0.04)	0.75 (±0.04)	0.88 (±0.03)
*F*u	0.43 (±0.04)	0.61 (±0.04)	0.72 (±0.03)
Paediatric data			
*F*d	0.58 (±0.18)	0.81 (±0.08)	0.94 (±0.06)
*F*u	0.57 (±0.05)	0.79 (±0.05)	0.91 (±0.03)
Laboratory tests			
*F*d	0.52 (±0.02)	0.76 (±0.03)	0.91 (±0.02)

Figure 3 shows a comparison between the *F*u curves for adult and paediatric data published previously [8, 9] and the *F*d curve for the laboratory data [17]. The corresponding *F*u values for the adult and paediatric data are noted also in table I. No significant difference between *F*u and *F*d from the paediatric study was seen, but *F*u from the adult study was significantly smaller ($P < 0.05$) than the corresponding *F*d values.

DISCUSSION

The results show that values of *F*d both in the laboratory study and the clinical studies are comparable. There was no statistically significant difference between the values of *F*d obtained at the $\dot{V}_E:\dot{V}_F$ ratios specified in table I in any of the three sets of data. All three sets predicted the maximum efficiency of the EAR to be approximately 0.94—a value which is in close agreement with the theoretical limit of 1.0 for a Mapleson A system.

The close agreement between *F*d and *F*u in children reflects a small end-tidal to arterial carbon dioxide partial pressure difference (0.23 kPa) and

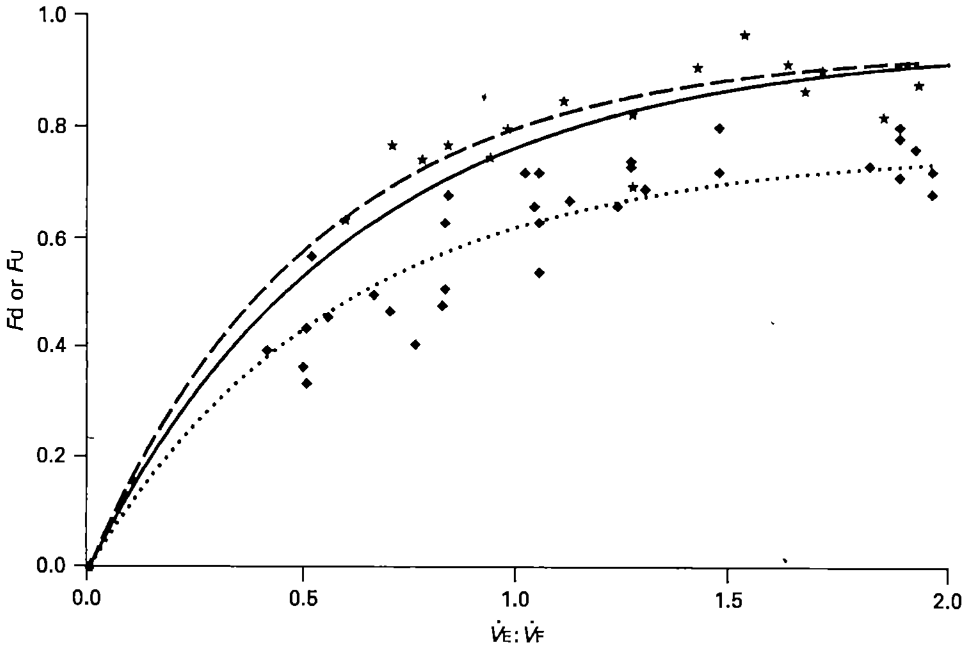

FIG. 3. *F*u data for adult (... ◆ ...) and paediatric (—★—) patients *vs* $\dot{V}_E:\dot{V}_F$ ratio and *F*d for the laboratory data (best fit line only —).

alveolar deadspace (4%) in these patients. In contrast, *F*U significantly underestimated the efficiency of the breathing system compared with *F*d in our elderly adult patients, who had a mean end-tidal to arterial carbon dioxide partial pressure difference of 1.03 kPa, corresponding to an alveolar deadspace of 19% [9]. Such changes are consistent with an increase in the $\dot{V}_D:\dot{V}_T$ ratio with age [13].

*F*d would appear to have several advantages over *F*U when the efficiencies of breathing systems are compared. It is relatively constant in different classes of patients and there is close agreement between clinical and laboratory determinations. Moreover, as it is calculated from end-tidal carbon dioxide concentration, a non-invasive clinical measurement, it is simpler to measure than *F*U.

*F*U may still be preferred for those studies designed to determine the fresh gas requirements of breathing systems, as these ultimately depend on the concentration of carbon dioxide in arterial blood. The relevance to the general anaesthetist is that, in practical terms, the end-tidal concentration may be significantly less than the arterial concentration when there is an increased alveolar deadspace. In healthy paediatric patients, in whom alveolar deadspace is small, any difference between the concentration of carbon dioxide measured at the connector end of a tracheal tube and that of the arterial blood is likely to be small and of little clinical significance.

ACKNOWLEDGEMENTS

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HEPATIC DISPOSITION OF METHOHEXITONE IN PATIENTS UNDERGOING CORONARY BYPASS SURGERY

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SUMMARY

In order to clarify the relative contribution of hepatic metabolism to the short term disposition of methohexitone, we have measured hepatic blood flow during induction of anaesthesia with a 1.5-mg kg^{-1} i.v. bolus dose of methohexitone. Median hepatic clearance was 1.01 litre min^{-1} and hepatic extraction 87%. As a consequence of the high hepatic extraction, the hepatic clearance of methohexitone was closely dependent on hepatic plasma flow. (Br. J. Anaesth. 1992; **69**: 478–481)

KEY WORDS

Anaesthetics, intravenous: methohexitone. Liver: blood flow, metabolism. Pharmacokinetics.

Methohexitone is a short acting barbiturate introduced into clinical anaesthesia in 1957 [1]. In contrast with thiopentone, it is characterized by rapid metabolism. However, the basis for its short action on induction of anaesthesia is its rapid distribution. While thiopentone is eliminated with a half-life of more than 6 h [2–4], the elimination half-life of methohexitone is 2–4 h. The relatively rapid elimination of methohexitone is reflected in the high total body clearance of more than 800 ml min^{-1} [5–7]. The relative contribution of the liver to the overall disposition in man, however, is not yet known. In order to clarify the site of disposition of methohexitone in man, we have studied patients who were undergoing cardiac surgery and receiving methohexitone for induction of anaesthesia.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and all patients gave written informed consent. We studied 10 male patients (table I) who were referred for elective coronary artery bypass surgery. All had involvement of one to three coronary vessels, but compensated ventricular function (ejection fraction range 0.71–0.46). Plasma concentrations of transaminases, alkaline phosphatase, gamma-glutamyl transpeptidase and bilirubin, and prothrombin time were within normal limits and revealed no evidence of liver disease.

Current medication was continued until the day before the operation. Premedication consisted of flunitrazepam 2 mg orally on the evening before operation and 1.5 h before induction of anaesthesia.

Immediately after arrival of the patient in the operating theatre, a blank plasma sample was taken and a venous indocyanine green (ICG) infusion was started through a 14-gauge cannula in a forearm vein. After cannulation of a radial artery, a 12-gauge catheter was inserted through the right internal jugular vein and positioned under fluoroscopic control into a right hepatic vein. Hepatic venous oxygen saturation was measured to verify the position of the catheter during the investigation. A 12-gauge pulmonary artery thermodilution catheter was inserted by a brachial vein and wedge position was verified by the pressure curve. After measurement of cardiovascular variables at rest (MPI), anaesthesia was induced with methohexitone 1.5 mg kg^{-1}, fentanyl 7 µg kg^{-1} and pancuronium 0.1 mg kg^{-1} i.v. Patients' lungs were ventilated mechanically and normoventilation was verified by blood-gas analysis and measurement of end-expiratory carbon dioxide. Anaesthesia was maintained with a constant infusion of fentanyl 20 µg min^{-1} and nitrous oxide in oxygen with $F_{I_{O_2}}$ 0.5. Immediately after injection of methohexitone, hepatic plasma flow and cardiovascular variables were measured again for 15 min and arterial and hepatic venous samples

TABLE I. *Patient data. D = Diltiazem; Dz = diazepam; F = fenofibrate; H = hydrochlorothiazide; ID = isosorbide dinitrate; M = molsidomine; N = nifedipine; S = sitosterine; T = triamterene*

Patient No.	Age (yr)	Height (cm)	Weight (kg)	Dose (mg)	Premedication
1	45	175	79	120	D,Dz,ID,S
2	55	172	77	115	ID,N
3	65	179	89	130	F,ID,N
4	41	183	92	140	D,S
5	58	165	65	100	D,H,ID,T
6	57	168	79	120	D,F,M
7	48	183	95	150	ID,N
8	63	173	84	130	ID,N
9	65	176	84	130	D,F,ID
10	48	178	88	130	F,D
n	10	10	10	10	
Median	56	176	84	130	

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were collected for measurement of plasma methohexitone concentrations (MPII). Before skin incision, a bolus dose of midazolam 5 mg was given to ensure hypnosis. The same measurements and blood samples as described for MPI and MPII were taken during sternotomy (MPIII).

Hepatic plasma flow was determined by the steady state infusion and extraction technique described by Bradley [8] using ICG as indicator. The infusion rate was 0.5 mg min^{-1} throughout the whole period of investigation and the ICG infusion was started at least 30 min before the first measurements in order to allow time for the achievement of steady state conditions.

Three arterial and three hepatic venous blood samples were collected alternately at intervals of 3 min and ICG plasma concentration was measured. If plasma concentrations of ICG changed less than 6% within the 15-min interval, steady state conditions were assumed and hepatic plasma flow was calculated.

Cardiac output (CO) was measured by the thermodilution method using an automatic device (Fischer HZV, Mod. BN 7260, Göttingen, FRG). Systemic and pulmonary artery pressures were recorded using Statham transducers.

Plasma analytical procedures

Heparinized blood 3 ml was centrifuged immediately after sampling and absorption measured photometrically at 800 nm within at least 3 h after sampling. The calibration curve consisted of concentrations of 50, 250, 750 and 1250 mg $litre^{-1}$ with an interday coefficient of variation of 4.2% ($n = 10$) at 50 mg $litre^{-1}$ and 3.9% ($n = 10$) at 1250 mg $litre^{-1}$.

Plasma concentrations of methohexitone were measured by gas chromatography with alkali flame ionization detection. This was a modification of the procedure described by Le Normand and colleagues [9]. The extraction was performed according to the method of Heusler and colleagues [10]. Plasma 1 ml was mixed with internal standard (propoxate) and solvent 10 ml (ether: n-hexan: isoamylalcohol 50:50:2). After centrifugation, the organic supernatant was evaporated to dryness under nitrogen. The residue was dissolved in ethanol 100 µl and injected into a capillary column (30 m DB-5, 0.32 mm i.d.). The temperature of the injector was 260 °C, that of the column 230 °C and of the detector, 250 °C. Helium was used as carrier with a flow rate of 3 ml min^{-1}. Retention times of methohexitone and internal standard were 6.25 and 11.55 min, respectively.

Limit of detection was 0.01 µg ml^{-1}. Quality control was performed with standard concentrations of methohexitone 0.5, 1.0 and 5.0 µg ml^{-1} in human plasma, which were added randomly to the patients' samples and prepared together. The interserial coefficient of variation was 5.4% at 0.5 µg ml^{-1}, 7.8% at 1.0 µg ml^{-1} and 3.6% at 5.0 µg ml^{-1} ($n = 10$ in all cases).

Calculations

Splanchnic oxygen consumption was calculated as the product of hepatic blood flow (hepatic plasma flow/1-PCV) and arterial–hepatic venous difference in oxygen content (LEX-O_2CON, IL).

Hepatic extraction of methohexitone was calculated as $E = (AUC_{art} - AUC_{hv})/AUC_{art}$, where AUC_{art} and AUC_{hv} = areas under the arterial and hepatic venous plasma concentration–time curves extrapolated to infinity, respectively. Extrapolation to infinity was performed in order to calculate total body clearance. The AUC were calculated by the iteration method with the Gauss–Newton algorithm using the PCNONLIN computer program (Statistical Consultants Inc., Lexington, Kentucky, U.S.A.). Weighting was 1/y. The extrapolated part of the AUC represented about 20% of the total arterial and hepatic venous AUC.

Hepatic clearance of ICG at steady state was calculated as the ratio of the infusion rate to the arterial plasma concentration. Hepatic venous concentrations of ICG could always be measured above the limit of detection. Total clearance of methohexitone (Cl^{tot}) was calculated as the ratio of the dose to the arterial AUC of methohexitone and hepatic plasma clearance (Cl_H) as follows: $Cl_H = Q_{H,P} \cdot E$, where $Q_{H,P}$ = hepatic plasma flow and E = hepatic extraction of methohexitone.

Results are presented as median values. Statistical analysis was performed using the Friedmann test comparing results before induction of anaesthesia (MPI) with those after induction (MPII) and the results of MPII with those at sternotomy (MPIII). Significant differences were assumed at $P < 0.05$.

RESULTS

All patients tolerated the investigation, without complication and were discharged from hospital after 2 weeks.

Haemodynamic data are shown in table II. Before induction of anaesthesia, median heart rate (HR) was 60 beat min^{-1}; it did not change significantly during the study. Median arterial pressure (MAP) decreased by 26% from 106 mm Hg after induction ($P < 0.01$) and returned to 95 mm Hg at sternotomy ($P < 0.01$). Cardiac output tended to decrease by 26% after induction and remained constant at sternotomy.

ICG extraction was 0.77 before induction and did not change significantly during the investigation. ICG plasma clearance did not change after induction but tended to decrease (10%) at sternotomy. The estimated hepatic plasma flow ($Q_{H,P}$) was 1.28 litre min^{-1} initially and did not change significantly after induction or at sternotomy. However, as expected from the results of ICG extraction and ICG clearance, $Q_{H,P}$ tended to decrease by 10% at sternotomy. Hepatic blood flow (Q_H) showed similar tendencies: it represented about 40% of cardiac output initially, 53% after induction ($P > 0.05$) and 41% at sternotomy. Hepatic oxygen consumption remained unchanged and was within normal physiological ranges.

Hepatic extraction of methohexitone was 0.87. Consequently, hepatic clearance of methohexitone was 1.01 litre min^{-1}, closely related to hepatic plasma flow.

TABLE II. *Haemodynamic data.* E_{ICG} = *Extraction of ICG*; Cl_{ICG} = *hepatic ICG clearance*; $Q_{H,P}$ = *hepatic plasma flow*; Q_H = *hepatic blood flow*; $\dot{V}H_{O_2}$ = *hepatic oxygen consumption*; *HR* = *heart rate*; *MAP* = *mean arterial pressure*; *CO* = *cardiac output*

	E_{ICG}	Cl_{ICG} (litre min^{-1})	$Q_{H,P}$ (litre min^{-1})	Q_H (litre min^{-1})	$\dot{V}H_{O_2}$ (ml min^{-1})	HR (litre min^{-1})	MAP (mm Hg)	CO (litre min^{-1})	Q_H (% CO)
Before induction (MPI)									
n	10	10	10	10	10	10	10	10	10
Minimum	0.58	0.70	0.92	1.88	69.60	43	89	4.01	30
Maximum	0.87	1.13	1.53	2.91	104.12	73	113	7.23	55
Median	0.75	0.95	1.28	2.46	97.93	60	106	6.11	40
After induction (MPII)									
n	10	10	10	10	10	10	10	10	10
Minimum	0.54	0.69	1.04	1.80	44.87	42	61	3.58	36
Maximum	0.87	1.16	1.71	2.95	114.50	69	94	5.22	69
Median	0.69	0.84	1.27	2.28	105.19	58	79	4.50	53
P vs MPI	ns	ns	ns	ns	ns	ns	< 0.002	ns	ns
At sternotomy (MPIII)									
n	10	10	10	10	10	10	10	10	10
Minimum	0.48	0.47	0.78	1.42	85.44	47	79	3.48	28
Maximum	0.80	0.99	1.29	2.97	119.69	71	130	6.67	60
Median	0.70	0.76	1.15	2.14	99.13	56	95	4.99	41
P vs MPII	ns	ns	ns	ns	ns	ns	< 0.01	ns	ns

DISCUSSION

This study has confirmed that methohexitone is subject to a very high hepatic extraction. Consequently, its hepatic elimination is dependent heavily on hepatic blood flow. Distribution into deep compartments, however, is relatively more important for the overall disposition of methohexitone than its clearance by the liver. As a result, the potential for drug accumulation after repeated or continuous dosing cannot be disregarded. These conclusions, however, must be viewed in the light of the limitations of the study.

For exact measurements of hepatic plasma flow, an accurate steady state must be achieved—that is, the infusion rate of the indicator and removal by the liver have to be equal. In our study, plasma concentrations remained relatively stable (±6%) during measurement of hepatic plasma flow, so correct steady state conditions can be assumed. Measurement of hepatic plasma flow with ICG using liver vein catheterization requires a hepatic extraction of more than 0.2 to give valid results [11]. This condition was fulfilled in our study. ICG is removed from the plasma by uptake into the hepatocyte and eliminated unchanged by canalicular excretion with the bile. Therefore, metabolic interactions between ICG and methohexitone may reasonably be excluded. External influences on haemodynamic variables also must be considered after induction of anaesthesia. Preoperative sympathetic cardiovascular responses are likely to be unimportant in our study because of effective premedication, although they cannot be excluded. All patients reached the operation area asleep and tolerated preoperative manipulations before induction of anaesthesia, including catheterization under local anaesthesia without significant cardiovascular reactions. The fact that hepatic blood flow was 40–50% of cardiac output indicates also pronounced parasympathetic activity in the absence of stress. Interference by ICG could be excluded also, as there is no evidence for direct cardiovascular effects of ICG, which is used widely for the measurement of cardiac output and hepatic plasma flow [8, 11].

To our knowledge, the contribution of the liver to the total clearance of methohexitone has not yet been reported. Richter and colleagues [6] reported a hepatic extraction of 0.67 for methohexitone. This difference from the value of 0.87 in our study can be explained by the limits of the method used by Richter's group, who investigated hepatic extraction by comparing parenteral and enteral methohexitone. This study design is limited by variations in intestinal absorption. Direct measurement of hepatic venous concentration of the drug, as performed in our study, is more reliable. Interactions in the elimination of methohexitone with intercurrent therapy are probably not important in our study. The therapy was discontinued the day before operation, so most of the drugs were eliminated by the day of investigation. No patient needed antianginal therapy in the period between stopping intercurrent therapy and beginning of anaesthesia. Finally, a theoretically possible interaction of elimination of methohexitone

TABLE III. *Pharmacokinetics*

Patient No.	$AUC_{art})$ (μg min^{-1} ml^{-1})	$AUC_{hv})$ (μg min^{-1} ml^{-1})	E	Cl_H (litre min^{-1})	Cl^{tot} (litre min^{-1})
1	86.48	7.27	0.92	0.96	1.39
2	92.25	24.41	0.74	0.95	1.25
3	99.16				1.31
4	113.88	8.31	0.93	1.04	1.23
5	80.48	7.74	0.90	1.12	1.24
6	103.41	8.26	0.92	1.09	1.16
7	94.62	18.63	0.80	1.13	1.59
8	129.25	28.21	0.78	0.98	1.01
9	96.51	16.20	0.83	0.98	1.35
10	86.32	20.81	0.76	0.98	1.51
n	10	9	9	9	10
Median	95.57	17.42	0.87	1.01	1.28

would lead to an underestimation of the extraction in our study, which would not affect our conclusions.

Total body clearance of methohexitone has been described by many authors; absolute values range between 818 and 910 ml min^{-1} [5–7]. Calculated total body clearance of methohexitone in our study was 1.28 litre min^{-1}. This difference can be explained by the calculation of clearance from the area under the plasma concentration–time curve (AUC) extrapolated to infinity. As a consequence of cardiothoracic surgery, the time of sampling was limited to about 80 min after induction of anaesthesia. Extracorporeal circulation leads to rapid haemodilution. This relatively short interval for the definition of the terminal phase of the plasma concentration–time curve results in a relevant error in the definition of the slope of the β-phase, underestimating the AUC extrapolated to infinity; this leads to overestimation of total body clearance. The data in the literature are based upon sampling intervals of more than 12 h, allowing a better definition of the terminal part of the plasma concentration–time curve. In the calculation of hepatic extraction, however, the error in the definition of the AUC is eliminated, because the amount of the area extrapolated to infinity is about 20% in both arterial and hepatic venous samples. We found hepatic blood flow represented 40–50% of cardiac output (table III). Normally, hepatic blood flow is only 20–30% of cardiac output. Thus hepatic clearance of methohexitone might be reduced under normal conditions. This reduced value of hepatic methohexitone clearance corresponds also with the data for total body methohexitone clearance reported in the literature. It can be concluded that the liver is the only organ responsible for the elimination of methohexitone in man.

The cardiovascular effects of methohexitone found in this study are compatible with the results obtained by other investigators [12–14]. Hepatic plasma flow remained unchanged after induction with methohexitone, as did splanchnic oxygen consumption. These effects may be the result of a pronounced parasympathetic activity after effective premedication.

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ANAESTHESIA FOR CRITICALLY ILL CHILDREN DURING MAGNETIC RESONANCE IMAGING

J. R. TOBIN, E. A. SPURRIER AND R. C. WETZEL

SUMMARY

Magnetic resonance imaging (MRI) is becoming increasingly useful in children. Because of technical considerations and safety concerns, critically ill children have frequently been excluded from MRI. We have accomplished safely both transport and MRI in 21 patients from paediatric intensive care units (ICU). Three children were not considered appropriate for transport from the ICU to the MRI facility. All patients underwent assisted ventilation using a modified Mapleson D system. Monitoring of oxygenation, ventilation and haemodynamic state, including invasive arterial ($n = 4$*) and intracranial pressures (*$n = 3$*) was continued successfully using routinely available equipment. All MRI studies were completed successfully with satisfactory image quality and all patients returned to the ICU in satisfactory condition. In contrast with previous reports which have excluded critically ill children, we have demonstrated that MRI may be undertaken safely and efficiently in critically ill children.* (Br. J. Anaesth. 1992; **69**: 482–486)

KEY WORDS

Anaesthesia: paediatric. Measurement techniques: nuclear magnetic resonance.

Magnetic resonance imaging (MRI) is used increasingly to improve accurate diagnoses [1–6], define plans for therapy [2] and provide new information on physiological changes [7–11] (table I). MRI examinations are of comparatively long duration, usually requiring 30–60 min of co-operation or immobility. The long cylindrical configuration of the MRI tunnel may be frightening to the conscious child and precludes visual assessment of the patient by personnel at the MRI control console. Monitoring equipment may malfunction in proximity to the magnet because of the high magnetic field strength and monitor wires may act as induction coils if looped, causing burns to the patient and poor scan quality [12]. In addition, ferrous objects brought into the scanning room may become dangerous missiles, potentially injuring the patient or attendants, or damaging the scanner [13, 14]. Ferrous and other metallic materials (praecordial stethoscope, subarachnoid bolts) in support and monitoring equipment, interfere with image generation of the MRI scanner [12]. These studies may also necessitate transportation to a site remote from the intensive care unit.

Patients who require airway control, assisted ventilation, supplementary oxygen, invasive monitoring, cardiovascular support, sedation or general anaesthesia for immobilization, pose challenging logistical problems. Critically ill patients must be monitored continuously and appropriately during MRI scanning, but there are some criteria for excluding patients (table II).

We describe our experience with monitoring of critically ill children during MRI.

PATIENTS AND METHODS

We studied 24 children, ages 3 days to 15 yr (2.5–60 kg), requiring paediatric intensive care, to assess if it was appropriate to obtain an MRI scan. Three patients were excluded because of severely labile intracranial hypertension, systemic hypotension and the presence of a cardiac pacemaker, respectively. The diagnoses of the 21 children deemed appropriate for study are detailed in table III. Of those 21, 18 required assisted ventilation (17 tracheal, one tracheotomy). In three patients the trachea was intubated to achieve airway control before transport and MRI. Therefore all MRI scans were obtained in patients with artificial airways. Three patients were receiving vasopressor agents. Invasive arterial ($n = 4$) and intracranial pressure ($n = 3$) monitoring were performed during transport and MRI. Informed consent for general anaesthesia and MRI was obtained from each patient's parent or guardian.

All MRI scans were performed using a 1.5 Tesla MR scanner (GE Signa or Siemens). The patient and accompanying anaesthetist were screened for ferrous objects using a hand magnet. All children were monitored constantly by an anaesthetist at the patient's side throughout transport and MRI, and kept warm by wrapping with loose fitting blankets. A hat or plastic covering was used over the scalp in infants. The ECG was monitored (Hewlett–Packard HP78352A) continuously during transport and MRI. Heart and breath sounds were monitored by the

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TABLE I. *Indications for MRI in critically ill children*

CNS imaging	Spinal cord imaging	Body imaging
Posterior fossa pathology	Injury	Airway malformations
Tumours, vascular, cerebellum	Myelopathies	Cardiac
Encephalopathies	Tumours	Tumours, congenital malformations
Encephalitis	Invasive, primary	Vascular anomalies and occlusions
Cerebritis		Systemic and pulmonary
Myelitis		Liver vascularity
Acute ischaemia		Preoperative vascular evaluation
Strokes		
Brain abscess		

TABLE II. *Criteria for exclusion from MRI scanning*

Unstable vital signs including severely labile intracranial hypertension
Permanent cardiac pacemaker
Temporary cardiac pacemaker
Automated internal cardiac defibrillator
Intravascular wire or transthoracic pacing wires
Neuroaneurysmal or vascular surgical clips (ferrous)
Intraocular metallic foreign body
Ferrous endoprostheses
Dependence on technology incompatible with MRI:
Extracorporeal membrane oxygenator, intra-aortic balloon pump, ventricular assist device

anaesthetist throughout the scanning process, with a plastic oesophageal stethoscope connected to a plastic earpiece. The patients' posterior tibial or dorsalis pedis pulses were palpated intermittently. The ECG and base unit of the end-tidal carbon dioxide ($P\text{E}'_{CO_2}$) monitor were located outside the MRI room with the video screens positioned at the radiofrequency (RF) screen window, easily visible to the anaesthetist in the MRI room. All the remaining monitors were located in the magnet room, beyond the 50-gauss line.

Pulse oximetry was used continuously throughout MRI scanning. The Nonin series 8604D (Nonin Medical, Plymouth, MN) oximeter was compatible with both the General Electric 1.5 Tesla and the

TABLE III. *Patients evaluated and subsequently supported for MRI scan. All patients were monitored with ECG, pulse oximetry, non-invasive arterial pressure (Dinamap) and a plastic praecordial or oesophageal stethoscope. Additional monitors used in selected patients: ICP = intracranial pressure; IA = invasive arterial; V = vasopressor support; CVP = central venous pressure. Other abbreviations: SVC = superior vena cava; CNS = central nervous system*

Age	Diagnosis	Comments
6 months	Pulmonary hypoplasia	Diagnostic information, therapeutic intervention
16 months	Arnold-Chiari malformation, basilar artery compression	Diagnostic information, surgical intervention
5 yr	Encephalopathy	Intubated for MRI, diagnostic information
4 yr	Congenital heart disease and SVC syndrome	Intubated for MRI, diagnostic information, therapeutic intervention
13 months	Apnoea, cervical cord compression	Diagnostic information, surgical intervention
5 yr	Closed head trauma	Diagnostic information
15 yr	Chemotherapy-induced spinal cord myelopathy, and encephalopathy	ICP, IA, V. Diagnostic information, therapeutic intervention
2 yr	Posterior fossa tumour	Diagnostic information, surgical intervention
14 yr	Subarachnoid haemorrhage	CVP, IA, ICP, V. Diagnostic information
7 months	Hydrocephalus	Surgical intervention
3 yr	Supratentorial astrocytoma	Diagnostic information, surgical intervention
2 months	Encephalopathy/encephalitis	Diagnostic information, therapeutic intervention
6 yr	Moyamoya arteritis and cerebral ischaemic accident	Diagnostic information
3 yr	Brain abscess	Diagnostic information, surgical intervention
4 weeks	Vocal cord paralysis, Arnold-Chiari malformation, hydrocephalus	Diagnostic information, surgical intervention
15 yr	Metastatic tumour to CNS, sepsis	IA, V. Diagnostic information, therapeutic intervention
5 yr	Supratentorial tumour, subdural hygromas	ICP, IA. Diagnostic information, surgical intervention
9 yr	Cerebellitis	Diagnostic information
3 days	Intracerebral cyst	Intubated for MRI. Diagnostic information, surgical intervention
13 yr	Extradural and parenchymal haematoma, closed head trauma	Diagnostic information, therapeutic and surgical intervention
10 yr	Brain abscess	Diagnostic information, surgical intervention

Siemens 1.5 Tesla MRI scanner. The oximeter did not cause degradation of the scan quality. $P\text{E}'_{\text{CO}_2}$ was measured by side-stream sampling to an Argon laser spectroscopy unit (Raman Spectroscopy, RASCAL, Albion, Salt Lake City, UT) with an easily visible digital and graphic display. For small infants (< 10 kg) a coaxial catheter (No. 12803, Dryden Corp., Indianapolis, IN), was inserted into the tracheal tube for gas sampling.

Arterial pressure was measured by the oscillometric method with a pneumatic cuff (Critikon-Dinamap 1846 SX Critikon, Inc., Tampa, FL) using 7.20-m long pneumatic tubing, at intervals appropriate for the patient's condition (range 3–10 min). The Dinamap was turned off during scans as it was known to interfere with image generation [personal observation]—during continuous ECG monitoring, an antennae effect occurs, thus drawing in radiofrequency interference from the electronic components of the Dinamap. Continuous intra-arterial pressure monitoring during MRI scanning ($n = 4$) required high-pressure, low compliance extension tubing connected to an arterial catheter, with the transducer placed at the level of the right atrium, beyond the 50-gauss line (Tektronix 412, Beaverton, OR, U.S.A.). This prevented the magnetic field from altering transducer performance.

Intracranial pressure was monitored in three patients. In two, an intraventricular catheter had been placed in the intensive care unit, and the pressure was monitored in a manner similar to i.a. pressure, utilizing low compliance extension tubing. The transducer and amplifier–monitor were kept beyond the 50-gauss magnetic field. The Camino 420 (Camino Laboratories, San Diego, CA) fibre-optic intraventricular catheter was used in another patient. The Camino computer unit is not MRI-compatible, therefore the catheter was connected to a closed drainage system with a "pop-off" pressure of 20 cm H_2O measured by the physician. In all three patients, intermittent readings (every 2 min) were taken with a manometer inserted into the line to confirm accuracy of transducer measurements.

All patients underwent ventilation via a tracheal tube throughout transport and MRI. Patients were transported using a standard self-inflating, manual ventilation device. As the MRI tunnel is several metres long, a Mapleson D breathing system constructed of plastic and non-ferrous materials was selected. This system comprised a Mapleson D disposable anaesthesia system with a 1-m respirator tube (41403E Marquest Medical Products, Englewood, CO, U.S.A.) to which we attached an additional 1-m length of corrugated tubing. A non-ferrous adjustable pressure relief valve (6140 Vital-Signs, Inc., Totowa, NJ, U.S.A.) was interposed between the system and an appropriately sized breathing bag. Oxygen from the central hospital supply was delivered to the fresh gas port on the airway connector via a length of universal gas tubing (Argyle, St. Louis, MO, U.S.A.). An additional 2.40-m length of this tubing was used to connect a pressure gauge for airway pressure monitoring (6098G Vital Signs, Inc., Totowa, N.J.) with the gauge positioned in direct view of the anaesthetist. Ventilatory compliance, airway leak and patency were assessed continually by the anaesthetist performing manual ventilation. An $F\text{I}_{\text{O}_2}$ of 1.0 was provided and PEEP 3–10 cm H_2O was regulated by the adjustable pressure relief valve and measured by the pressure gauge within the system. The minimal fresh gas flow which prevented rebreathing of expired carbon dioxide (as determined by capnography) during controlled ventilation was used (range 1–3 × the calculated minute ventilation) [15]. A disposable heat and moisture exchanger (Humid-vent, Gibeck Respiration, Vasby, Sweden) was added to the circuit to reduce heat and moisture loss from the airway.

Vasopressor support was required in three patients. Continuous infusions of vasoactive drugs were maintained with the use of a volumetric pump system (IMED, San Diego, C.A.), placed on an aluminum pole with an appropriate length of i.v. extension tubing. Previous experience with this pump demonstrated accurate delivery of fluid infusion when located beyond the 50-gauss line [data on record, The Johns Hopkins Hospital, Department of Clinical Engineering]. Administration of the vasoactive agents was assured by the use of a carrier or "piggy-back" system, which provided a carrier i.v. fluid in parallel at a rate greater than the pressor infusion rate.

I.v. anaesthetic agents were titrated to patient need and included thiopentone 5–8 mg kg^{-1} (induction) and pentobarbitone 0.5–2 mg kg^{-1}, ketamine 0.1–1.0 mg kg^{-1} over 10 min and propofol 0.10–0.30 mg kg^{-1} min^{-1}. Neuromuscular block was provided ($n = 10$) to ensure immobility (vecuronium 0.1 mg kg^{-1} and atracurium 0.5 mg kg^{-1}).

After completion of the MRI scan, the patients were returned to the intensive care unit. Upon arrival, vital signs were obtained and care transferred to the ICU staff.

RESULTS

Twenty-one of 24 patients (87%) evaluated were monitored and supported, and the MRI scans completed successfully. All patients remained haemodynamically stable throughout transport and MRI. Oxygen saturation was > 95% at all times. Ventilation was controlled easily or assisted in all children. End-tidal carbon dioxide analysis was accurate within 0–1 kPa when blood-gas analysis was performed simultaneously ($n = 4$). No changes in vasopressor dose were necessary throughout transport and MRI. On return to the intensive care unit, all patients had stable vital signs. The core temperature was within ±1 °C of the temperature before transport. A single complication, monitor battery failure, occurred during return transport to the ICU. The child suffered no ill consequences.

The quality of all images obtained was considered high by the reviewing radiologist. Results of the MRI scans obtained were consistent with the clinical diagnosis of the ICU team and referring physicians. In 11 patients, the MRI results were of value in decisions regarding surgical intervention. In eight patients the MRI results were superior to computed tomography scans obtained previously and follow-up MRI was performed as the diagnostic imaging technique of choice after discharge of the patient from the intensive care unit.

DISCUSSION

MRI has become a valuable diagnostic tool in many patients, including neonates with brainstem anomalies, children with cervical spine anomalies and spinal dysraphism [1, 2], airway assessment [3, 4], congenital heart disease [11], vascular occlusions, neoplastic disorders, spinal cord myelopathy and other conditions [6] (table I). With the use of modern monitoring technologies, airway control, supported ventilation and continuous observation by an anaesthetist, MRI need not be excluded in critically ill infants and children.

Recent reviews of anaesthesia for MRI do not make specific recommendations or report care of critically ill children for MRI [15–18]. It was necessary for us to exclude three children (13%): one had severe intracranial hypertension, another developed systemic hypotension and was deemed unsuitable for transport and a third child was excluded because of the presence of a pacemaker and previous reports of pacemaker malfunction in proximity to MRI scanners [16, 19].

The high intensity magnetic fields used in MRI pose problems, as noted in recent excellent reviews [16, 17, 19]. MRI uses a high intensity static magnetic field which attracts ferrous materials which may act as high velocity missiles, or crush a patient or attendant. In addition, the static magnetic fields distort the electron beams on video displays or oscilloscopes. ECG T-wave abnormalities have been noted in proximity to high intensity static magnetic fields; this is thought to be caused by interactions of the magnetic field with circulating blood, and is not a true biological effect [19]. Health risks associated with high intensity magnetic fields continue to receive a great deal of attention; however, no conclusive evidence exists regarding hazardous occupational exposure to MRI [16, 19].

After the patient is placed in the static magnetic field, radiofrequency pulsing (rapid changes in the magnetic field) is used to deflect the aligned axes of atoms. As the atoms return to alignment in the static fields (pulse off), energy is liberated. This energy is detected, information processed and imaging accomplished. The rapidly changing magnetic fields are accompanied by loud dull "clunking" noise which may obscure breath and heart sounds. However, use of an appropriate size oesophageal stethoscope permits breath and heart sounds to be heard almost continuously with a tight fitting earpiece. This RF pulsing generates electrical current and heat which may be conducted internally (pacemaker wires). Also, these RF pulses generate interference and artefact with conventional oscilloscopes [20], requiring the monitors be placed at a distance beyond interference or heavily shielded.

Monitoring patients during MRI should include ECG, pulse oximetry, end-tidal carbon dioxide analysis, and invasive arterial and intracranial pressure monitoring (when necessary). Patteson and Chesney have recently reviewed reports of equipment found compatible with MRI scanners [16]. We report the use of raman spectroscopy during MRI, thus demonstrating the feasibility of continuous $P\text{E}'_{CO_2}$, $F\text{I}_{O_2}$ and anaesthetic vapour concentration measurement during imaging. Although the magnetic field may interfere with monitoring devices, we found that placing transducers and monitors beyond the 50-gauss magnetic field intensity range provided accurate monitoring with only minor or tolerable loss of fidelity. No monitor was drawn to the magnet from this distance.

Intracranial pressure monitoring during MRI has been described previously [20]. In this report the authors describe their experience with intracranial pressure monitoring via an intraventricular catheter in neurological and neurosurgical patients. As measurement of intracranial pressure by mechanical methods (hydrostatic manometry) is not affected by magnetic fields, an intraventricular catheter can be used successfully throughout MRI. Here we report the use of the Camino fibreoptic catheter device (by its hydrostatic drainage system) in the MRI suite. Neither image quality nor transducer function was altered.

Anaesthesia was maintained i.v. in all children. Inhalation anaesthesia may be administered in the MRI suite, but additional technical problems are involved [12, 21–23]. These include scavenging of nitrous oxide and volatile anaesthetics, use of an oxygen analyser and purchase of non-ferrous anaesthetic equipment and gas cylinders.

Adults undergoing MRI have been supported successfully using non-ferrous ventilator technology (Monaghan 225, Monaghan Medical Corp., Plattsburgh, NY) [20] and a standard ventilator (Servo Ventilator 900C, Siemens-Elema AB, Solna, Sweden) with placement of the ventilator 1.20 m from the MRI tunnel and the use of shielding. Use of these ventilators in infants and small children is cautioned, as the circuits have significant compression volumes, high compliance and difficulty in accurately providing small tidal volumes; however, many of these problems may be minimized using a Bain circuit. Use of a non-ferrous mechanical ventilator for a child has been reported; nevertheless, we prefer and recommend manual ventilation, as this provides continuous, instantaneous feedback and monitoring by the attending physician.

Davis and colleagues [15] reported their experience of general anesthesia in 20 paediatric outpatients who had failed two sedation attempts. General anaesthesia with tracheal intubation was administered. Two attendants (excluding the scan technician) were involved with each patient: one at the patient's side in the scan room for drug administration and monitoring, and the other in the adjacent control room manually assisting ventilation from a remote distance. Boutros and Pavlicek reported the use of the Mapleson D system and combined inhalation and i.v. anaesthesia to support eight non-critically ill children during MRI [24]. In contrast with other authors, we have found breath and heart sounds audible throughout scanning when an oesophageal stethoscope is used. In our experience, a single anaesthetist could maintain assisted ventilation and i.v. anaesthesia while assessing monitors appropriately positioned.

Previous reports of support and monitoring to accomplish MRI in critically ill patients have been described for adults [14, 20]. In addition to the unique problems associated with MRI, transport of critically ill patients may involve significant risks. The incidence of mishaps has been reported to be as great as 34% [25, 26]. Physiological stability should be optimized before transport. Furthermore, co-ordination with the MRI facility to prevent delays when the patient has reached the site may decrease the incidence of mishaps [26]. In this study, the only mishap which occurred was loss of battery power to transport monitors *en route* from MRI to the intensive care unit.

As MRI suites may be in a location remote from the intensive care units, planning and preparation for transport and support of a critically ill child for MRI necessitates the availability of the complete range of resuscitation equipment, including emergency drugs.

There are contraindications to MRI in children, as noted in table II. Patients with ventriculo-peritoneal shunts should be screened for the content of metal in their shunt, before MRI is planned; however, most current shunts are MRI-compatible.

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INTERACTION BETWEEN HALOTHANE AND MU, DELTA AND KAPPA OPIOID AGONISTS ON THE ISOLATED RIGHT ATRIA OF THE RAT

J. A. MICOL AND M. L. LAORDEN

SUMMARY

We have examined the interaction between halothane and specific opioid agonists at mu (morphine and [D-ala^2 N-mephe^4, gly-ol^5]-enkephalin (DAGO)), delta ([D-pen^{2,5}]-enkephalin (DPDPE)) and kappa (trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolikynyl)cyclohexyl]-bencetamide methane sulphonate (U-50,488H)) receptors on the isolated right atria of the rat. All the opioid agonists tested decreased atrial rate. The maximal effects obtained with U-50,488H (75 (SE 3.3)%) were significantly ($P < 0.001$) greater than those obtained with morphine (12 (2.7)%), DAGO (8 (0.6)%) or DPDPE (11 (1.8)%). Halothane 1.5 v/v% did not modify the inhibitory effects induced by morphine, DAGO or DPDPE. However, U-50,488H had a potentiating effect in the presence of halothane 1.5 v/v% ($P < 0.001$). Naloxone 5×10^{-7} and 1×10^{-6} mol litre^{-1} antagonized the inhibitory effects of U-50,488H in the presence of halothane. We conclude that halothane increased the potency of a kappa agonist on isolated right atria and suggest that this effect was mediated by opioid receptors. (Br. J. Anaesth. 1992; **69**: 487–491)

KEY WORDS

Anaesthetics, volatile: halothane. Analgesics: DAGO, DPDPE, U-50,488H, morphine. Interactions (drug). Receptors: opioid.

In vivo [1, 2] and *in vitro* [3, 4] studies have demonstrated that inhalation anaesthetics produce direct negative chronotropic and inotropic effects. However, the specific sites and mechanisms of their action are not well established. Potential mechanisms of action for inhalation anaesthetics in cardiac cell have been proposed: slowing of calcium flux through voltage-gated calcium channels [5]; a change in calcium flux between myoplasm and sarcoplasmic reticulum or other intracellular pools [6] and interaction between the anaesthetic drug and protein molecules [7, 8]. In addition, it has been suggested [9] that halothane interacts with a specific type of membrane protein, the guanine nucleotide-binding proteins (G proteins). It is becoming increasingly evident that opioid receptors are functionally linked to G proteins [10]. Moreover, there is evidence for the presence of different subtypes of opioid receptor (mu, delta and kappa) in heart muscle—both in the atria and in the ventricles [11, 12].

The aim of the present study was to investigate the interaction between halothane and specific opioid agonists on spontaneous atrial rate by using selective agonists: morphine (preferential mu agonist), [D-ala^2 N-mephe^4, gly-ol^5]-enkephalin (DAGO—specific mu agonist), [D-pen^{2,5}]-enkephalin (DPDPE—specific delta agonist) and trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolikynyl)cyclohexyl]-bencetamide methane sulphonate (U-50,488H—specific kappa agonist) and naloxone—a non-specific antagonist.

MATERIALS AND METHODS

Isolated right atria were taken from Sprague–Dawley rats ($n = 88$) of both sexes (weight 150–200 g) killed by a blow on the head and immediate decapitation. The chest was opened with a midsternal incision and the right atrium isolated by a technique similar to that described previously [13]. The right atrium and sino-atrial node were suspended in a 10-ml organ bath. Tyrode solution of the following composition (nmol litre^{-1}) was used: NaCl 136.9; KCl 5.0; $MgCl_2$ 1.05; NaH_2PO_4 0.4; $NaHCO_3$ 11.9; $CaCl_2$ 1.8; glucose 5.0. The bathing solution was maintained at 37 °C and pH 7.4 and bubbled with 5% carbon dioxide in oxygen. When halothane was used, the carbon dioxide–oxygen mixture was passed through a Fluotec Mark II vaporizer and the delivered concentration of halothane verified by gas chromatography. The right atrium was beating spontaneously and was suspended under a resting tension of 0.5 g and equilibrated for 30 min before the start of the experiments. The frequency of spontaneous contractions was measured using a force–displacement transducer (Grass FT-03) and recorded on a Dynograph Beckman polygraph. Halothane was delivered to the organ bath in a concentration of 1.5%. When halothane became effective, the preparation was equilibrated for an additional 15 min in the presence of the anaesthetic. The halothane concentration remained unchanged throughout each experiment.

Increasing concentrations of morphine, DAGO, DPDPE or U-50,488H were added cumulatively to

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TABLE I. *Effects of halothane on auricular automaticity (mean* (SEM)) *compared with control* (= *100* %) *(before halothane).* n = *8 for each set of experiments.* *P *<0.05 compared with control*

	Change in automaticity (% of control)					
Control automaticity (beat min^{-1})	Halothane concentration (%)					
	0.3	0.5	1.0	1.5	2	2.5
248 (1)	100 (2.1)	100 (2.5)	98 (2.2)	97 (2.2)	96 (2.2)	94 (2.1)*

the organ bath in volumes of 0.1 ml. Concentration–response curves were obtained at concentrations between 1×10^{-11} and 5×10^{-4} mol litre^{-1} in the absence or presence of 1.5% halothane. In some experiments, different concentrations of naloxone (5×10^{-7} or 1×10^{-6} mol litre^{-1}) were added directly to the bath during the initial equilibration period and were present throughout the experiment. Control concentration–response curves were obtained for 0.1%, 0.3%, 0.5%, 1%, 1.5%, 2% and 2.5% halothane and naloxone (data not shown). Each drug concentration was added to the organ bath at 3-min intervals. Control experiments without drugs showed that the frequency of contractions did not change.

The drugs used in this study were halothane (ICI), morphine hydrochloride (Alcaliber), DAGO ([D-Ala^2 N-Mephe^4, Gly-ol^5]-enkephalin, Penisula), DPDPE ([D-pen^{2,5}] enkephalin, Penisula), U-50,488H (trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolikynyl)cyclohexyl]-bencetamide methane sulfonate (a gift from Upjohn)) and naloxone hydrochloride (a gift from Merck, Sharp & Dohme). All drugs were dissolved in distilled water.

The effects of halothane or opioid agonists alone are expressed as percent changes from the baseline values. Similarly, the effects of U-50,488H in the presence of halothane or in the presence of halothane plus naloxone are expressed as percent changes from the baseline values after halothane or halothane with naloxone. To compare the inhibitory effects of U-50,488H in the absence or in the presence of halothane or halothane with naloxone, we measured the 50% inhibitory concentration (CI$_{50}$) for each set of experiments.

Data were examined by analysis of variance with Student's *t* test for individual comparison. The IC$_{50}$ was calculated by linear regression of the log-concentration plot of the data with the aid of a computer program [14]. $P < 0.05$ was considered significant.

RESULTS

Halothane 0.3–1.5% did not change auricular automaticity compared with the control (table I). However, it produced a small (6 (1.6)%, maximum) but significant ($P < 0.05$) effect at the greatest concentration tested (2.5%).

The data obtained for morphine, DAGO and DPDPE with or without 1.5% halothane are shown in table II. This concentration of halothane alone produced a small (3%) but not significant decrease in auricular chronotropism (table I). Morphine alone did not alter atrial chronotropism at concentrations of 1×10^{-11} to 1×10^{-5} mol litre^{-1}. However, morphine 5×10^{-4} mol litre^{-1} produced a small (12 (2.7)% maximum) but significant ($P < 0.05$) decrease. When 1.5% halothane was present in the organ bath, morphine 5×10^{-4} mol litre^{-1} increased auricular automaticity (table II). Halothane did not modify the chronotropic effects induced by DAGO or DPDPE. All tested concentrations of DAGO induced a significant decrease ($P < 0.05$) in auricular chronotropism. The maximal effect (8 (0.6)%) was obtained with 5×10^{-4} mol litre^{-1}. Similar results were obtained when 1.5% halothane was present in the organ bath. In this case the maximal effect was 10 (1)%—similar to that found with DAGO alone (table II). DPDPE 1×10^{-7} to 5×10^{-4} mol litre^{-1} induced a significant ($P < 0.05$) decrease in auricular chronotropism compared with control. The maximal effect was 11 (1.8)%, similar to that described with DAGO or morphine. Halothane 1.5% did not modify the auricular chronotropism induced by DPDPE. When halothane was present in the organ bath, the maximal effect obtained with DPDPE was 5 (1.2)% (table II).

Concentration–response curves for U-50,488H obtained in the absence and in the presence of halothane or halothane with naloxone are illustrated in figure 1. U-50,488H alone significantly decreased the frequency of contraction at concentrations from 1×10^{-8} to 5×10^{-4} mol litre^{-1}. U-50,488H 5×10^{-4} mol litre^{-1} induced a significant ($P < 0.01$) negative chronotropic effect compared with the control. The maximal effect was (75 (3.3)%). Halothane 1.5% modified the maximal negative chronotropic response to U-50,488H. In the presence of halothane, U-50,488H 1×10^{-5} mol litre^{-1} was capable of producing a 100% inhibition of auricular frequency. At this concentration, U-50,488H alone produced a reduction in auricular chronotropism (14 (1.8)%) significantly ($P < 0.001$) less than that obtained with U-50,488H in the presence of halothane (100 (0)%).

We obtained concentration–response curves for U-50,488H in the presence of halothane and naloxone to determine whether naloxone antagonizes the effects of U-50,488H on auricular chronotropism in the presence of halothane (fig. 1). The concentrations of naloxone (5×10^{-7} or 1×10^{-6} mol litre^{-1}) used in these experiments were devoid of effect on auricular frequency. The maximal effect obtained with U-50,488H 1×10^{-5} mol litre^{-1} in the presence of halothane was 100 (0)%. Naloxone progressively reduced this effect (57 (2.3)% and 21 (1.2)% in the presence of naloxone 5×10^{-7} and 1×10^{-6} mol litre^{-1}, respectively).

The concentrations of U-50,488H that caused a 50% of inhibition in the auricular chronotropism

TABLE II. *Effects of morphine (M), DAGO and DPDPE in the absence or presence of 1.5% halothane (H) on auricular automaticity (mean (SEM)) compared with control (= 100%) (before halothane).* n = *8 for each set of experiments.* *P < *0.05*; **P < *0.01 compared with control*

Drug	Control automaticity (beat min^{-1})	Change in automaticity (% of control)							
		−Log concentration of drug (mol litre^{-1})							
		10	9	8	7	6	5	4	3.30
M	251 (2.0)	100 (0)	99 (1.7)	100 (3)	99 (2.8)	97 (4.3)	94 (4.4)	89 (4.4)	88 (4.1)*
M+H	249 (0.9)	94 (3.9)	94 (4.4)	98 (7.2)	98 (7.8)	98 (6.6)	98 (6.7)	105 (6.6)	111 (7.5)
DAGO	245 (0.9)	97 (0.5)*	97 (0.8)*	96 (1)*	94 (0.9)*	94 (1)*	93 (1.2)*	92 (0.7)**	92 (0.1)**
DAGO+H	243 (1.3)	97 (1.8)	96 (2)	94 (2.5)	94 (2.7)	95 (3)	94 (3.4)	90 (4.7)	90 (3.1)*
DPDPE	255 (2.6)	98 (2)	96 (2.2)	94 (2.6)	92 (1.4)*	90 (1.9)*	92 (2.6)*	89 (3.7)*	89 (3.0)*
DPDPE+H	247 (2.1)	97 (1.2)	98 (1.1)	97 (0.7)*	96 (1.2)	96 (1.2)	95 (1.7)*	95 (1.7)*	95 (1)*

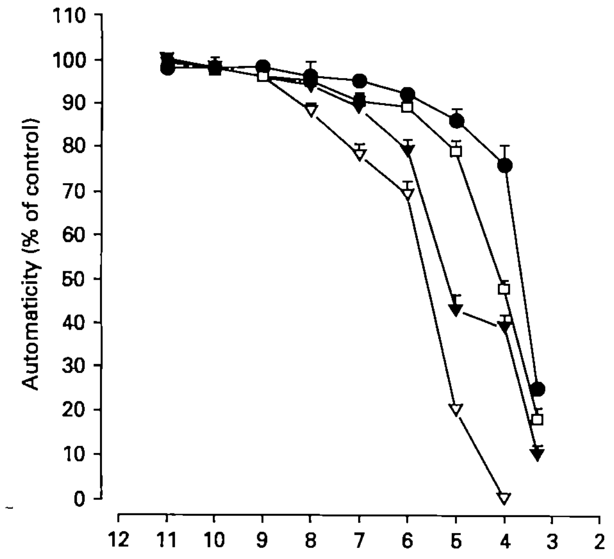

FIG. 1. Effect of U-50,488H on atrial rate in the absence (●; control rate (before halothane) 251 (1.8) beat min^{-1}) or in the presence of halothane (▽; control rate 255 (2.1) beat min^{-1}), halothane with naloxone 5×10^{-7} mol litre (▼; control rate 249 (1.8) beat min^{-1}) or halothane with naloxone 1×10^{-6} mol litre^{-1} (□; control rate 250 (1.2) beat min^{-1}). Each point represents mean, SEM. *n* = 8 for each set of experiments.

TABLE III. *IC$_{50}$ for U-50,488H on isolated right atria in the absence and the presence of 1.5% halothane (H) or halothane with naloxone (Nx).* n = *8 for each group. †Compared with U-50,488H alone*

Drug	IC$_{50}$ U-50,488H ($\times 10^{-5}$ mol litre^{-1})	*P*†
U-50,488H	61.0 (4.0)	—
U-50,488H+H	0.5 (0.01)	< 0.001
U-50,488H+H+Nx 5×10^{-7} mol litre^{-1}	2.0 (0.02)	< 0.001
U-50,488H+H+Nx 1×10^{-6} mol litre^{-1}	30.0 (2.0)	< 0.05

(IC$_{50}$) in the absence or presence of halothane or halothane with naloxone are given in table III. Halothane increased the potency of U-50,488H significantly.

DISCUSSION

In order to avoid extrinsic mechanical, nervous and humoral factors that are difficult to control in *in vivo* experiments, we have used the isolated right atrial preparation to study the effects of morphine (preferential mu agonist), DAGO (specific mu agonist), DPDPE (specific delta agonist) and U-50,488H (specific kappa agonist) and the interaction between halothane and specific opioid agonists. This method has been used widely to evaluate the actions and interactions between different drugs on chronotropic automaticity [13, 15].

Morphine, DAGO, DPDPE and U-50,488H caused a direct negative chronotropic effect on the isolated right atrium, in agreement with the results of other studies [16–19]. The inhibitory effect of U-50,488H was consistently greater than that of morphine, DAGO or DPDPE, suggesting that the kappa opioid receptors are those principally implicated in the negative chronotropic effects induced by opioid agonists.

Our results also showed that halothane had a direct negative chronotropic action, in agreement with other *in vitro* studies [20, 21]. Although the precise mechanisms by which halothane produce a negative chronotropic effect in normal cardiac muscle are not well established, several different mechanisms of action have been proposed: impairment of excitation–contraction coupling in the myocardium by reduction of the influx of extracellular Ca^{2+} and the amount of Ca^{2+} in the intracellular stores, leading to a decrease in calcium ions available for activation of myocardial contraction [22, 23]; reduction of ATPase activity in the myofibrils [7]; interaction with G proteins [9]. It is known that opioid receptors are functionally linked to G proteins [10] and it is possible that the chronotropic effects of halothane are mediated by these receptors. A previous report from our laboratory demonstrated that naloxone antagonized the cardiac effects of halothane [24].

The major aim in our study was to investigate the combined direct effects of halothane with morphine, DAGO, DPDPE or U-50,488H on spontaneous sino–atrial rate. Using isolated right atria, in which opioid receptors are present [11, 12], we have demonstrated that U-50,488H has a potentiating effect in the presence of halothane. However, halothane did not modify the potency of morphine, DAGO or DPDPE. Our results indicate that halothane and U-50,488H could interact in a synergistic manner. These results are consistent with those of other investigators [25] who reported an interaction between halothane and opioids *in vivo*.

An interaction between halothane and morphine has been demonstrated in longitudinal muscle preparations of guineapig myenteric plexus [26] and in isolated left atria [27]. However, in the present study halothane did not change the effects of morphine, DAGO or DPDPE. The difference observed between these experiments and the present results could be attributable to the nature of the preparation used in this study. The sympathetic axons innervating the sinus node of the rabbit possess presynaptic opioid kappa, but not mu or delta, receptors [28]. Similar results were obtained in guineapig atrial noradrenergic nerves [29].

Diltiazem, a calcium channel antagonist, usually augments, but in the presence of an increased calcium concentration inhibited, the cardiac effect induced by halothane [20]. Opioid binding to specific receptors on the cellular membrane triggers a variety of changes, through G proteins, such as inhibition of ionic conductance [30, 31]. It has been established that mu, delta and kappa receptors are coupled differentially to ionic conductances [31]. Thus mu and delta receptors have been shown to be coupled to K^+ conductance, while the kappa receptors cause a reduction in voltage-dependent Ca^{2+} conductance [32, 33]. These observations support our hypothesis that halothane and U-50,488H could interact in a synergistic manner. Furthermore, naloxone antagonized the interaction between halothane and U-50,488H in a dose-related manner in our preparation, indicating that the interaction between halothane and U-50,488H could be related to events occurring at the opioid receptor complex.

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ENHANCEMENT OF BUPIVACAINE TOXICITY BY DILTIAZEM IN ANAESTHETIZED DOGS[†]

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SUMMARY

We have studied the cardiovascular effects of graded doses of bupivacaine in the absence or presence of clinical concentrations (approximately 250 µg litre^{-1}) of diltiazem in fentanyl–pentobarbitone anaesthetized dogs. Bupivacaine was given, increasing in a stepwise manner, as a loading dose (200, 400 or 600 µg kg^{-1}) followed by a 30-min i.v. infusion (25, 100 or 200 µg kg^{-1} min^{-1}, respectively). Thereafter, bupivacaine was infused at 400 µg kg^{-1} min^{-1} until each animal died. Group A (n = 7) received bupivacaine, group B (n = 5) diltiazem (400 µg kg^{-1} followed by 12 µg kg^{-1} min^{-1}) and group C (n = 7) received diltiazem followed by bupivacaine given as in group A. Lethal plasma concentrations of bupivacaine were significantly smaller ($P < 0.01$) in group C (7.1 (SEM 0.7) vs 12.6 (1.5) mg litre^{-1}). Bupivacaine produced similar decreases in cardiac index, left ventricular (LV) segmental work and the first derivative of LV pressure (LV dP/dt) in the absence and presence of diltiazem. In group A, bupivacaine increased systemic vascular resistance index (SVRI) and thus mean arterial pressure (MAP) was maintained. In group C, SVRI, reduced by diltiazem per se, *did not increase in response to bupivacaine, so MAP was not maintained. Death resulted from a progressive decrease in cardiac contractility and MAP. Plasma concentrations of bupivacaine attained at the three doses were similar in the absence and presence of diltiazem. This study has shown that the toxicity of bupivacaine was increased approximately two-fold by diltiazem.* (Br. J. Anaesth. 1992; **69**: 492–497)

KEY WORDS

Anaesthetics, local: bupivacaine. Heart: cardiovascular toxicity, diltiazem.

Bupivacaine decreases cardiac contractility in a dose-dependent manner. While this probably results primarily from Na^+ channel block [2], bupivacaine also appears to block Ca^{2+} channels and may decrease release of Ca^{2+} from the sarcoplasmic reticulum [3]. Additive cardiovascular depression has been observed in conscious dogs treated with combinations of bupivacaine and the phenylalkylamine calcium antagonist, verapamil [4]. A brief clinical report of a probable adverse interaction between bupivacaine and verapamil has also been published [5]. In contrast, nicardipine, a dihydropyridine calcium channel antagonist, with relatively selective effects on arterial resistance vessels, appears to be protective against bupivacaine toxicity in the rat [6]. Diltiazem, a benzothiazepine calcium antagonist, has effects on the cardiovascular system intermediate between those of verapamil and nicardipine and is used frequently in the treatment of angina and hypertension [7]. It is not known if diltiazem also interacts adversely with bupivacaine.

This study was designed to assess the pharmacodynamic interaction between bupivacaine and diltiazem, by measuring their effects alone and in combination, on regional and global cardiac function in anaesthetized dogs.

MATERIALS AND METHODS

Approval for animal use in this study was granted by the Health Sciences Animal Care Committee of the University of Alberta. Experiments were performed on conditioned mongrel dogs (24–31 kg). Anaesthesia was induced with pentobarbitone 30 mg kg^{-1} and mechanical ventilation with an oxygen-enriched air mixture was adjusted to maintain normal end-tidal carbon dioxide concentrations. After administration of fentanyl 40 µg kg^{-1} and pancuronium 80 µg kg^{-1}, anaesthesia was maintained by a constant infusion (4 ml kg^{-1} h^{-1}) of fentanyl 20 µg kg^{-1} h^{-1}, pentobarbitone 3 mg kg^{-1} h^{-1} and pancuronium 60 µg kg^{-1} h^{-1} in 0.9 % sodium chloride. A pulmonary artery thermodilution catheter was introduced via the right external jugular vein and a precalibrated high fidelity pressure transducer tipped catheter was positioned in the left ventricle (LV) via the right femoral artery for measurement of LV pressure and the first derivative of LV pressure (LV d*P*/d*t*). A bipolar pacing electrode was placed in the right atrium via a femoral vein. After a left lateral thoracotomy, two piezoelectric crystals (5 MHz, 1.5–2.0 mm diameter) were inserted into the sub-

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endocardium of the LV so that myocardial segment length (SL) could be measured continuously. After instrumentation, positive end-expiratory pressure (5 cm H_2O) was applied to the airways to prevent atelectasis. Arterial blood-gas tensions, serum electrolyte concentrations and acid–base state were measured at regular intervals. Sodium bicarbonate and potassium chloride were infused, as required, to prevent development of acidosis or hypokalaemia, respectively.

Heart rate (HR), ECG, arterial pressures, SL, LV pressures (LVP) and LV dP/dt were measured continuously. PR intervals were measured from high speed recordings (100 mm s^{-1}) during 15-s periods of atrial pacing at 2.5 Hz. Cardiac output was determined by thermodilution (Edwards cardiac output computer), each value being the average of four individual measurements. Stroke index (SI), cardiac index (CI) and systemic vascular resistance index (SVRI) were calculated from standard formulae [8]. SL between the pair of LV crystals was measured at end-diastole and at the time of maximal shortening during systole and percent segment shortening during systole (%SS) was calculated. LVP–SL loops were constructed for measurement of pressure–length areas, an index of LV segmental work (LVSW).

Blood samples (5 ml) were collected into heparinized blood collection tubes and plasma was separated and stored at −20 °C until analysis. Plasma concentrations of bupivacaine and diltiazem were analysed by an HPLC method developed in our laboratory. An internal standard, benzyl amphetamine 50 µl of 20 µg ml^{-1} was added to 0.5 ml of each plasma sample. The mixture was vortexed with ethyl acetate 4 ml for 15 min on a vortex shaker and centrifuged at 1000 *g* for 10 min. The aqueous layer was frozen on a dry ice–acetone bath, then the organic phase was removed and back-extracted with 0.4 ml of hydrochloric acid 0.01 mol $litre^{-1}$. The organic phase was again removed as above and the aqueous layer was placed under a gentle stream of nitrogen for 5 min. Fifty microlitre of the extract was injected onto a Waters HPLC system (Waters, Mississauga, Ont.) with a u.v. detector set at 214 nm. Separation was achieved by running a mobile phase, consisting of acetonitrile, a mixture of 0.092% orthophosphoric acid and 0.2% triethylamine in water (36:62% v/v), at 2 ml min^{-1} through a Waters Novapak C_{18} radial-pak cartridge (4 µm, 8 mm × 10 cm). Calibration curves, constructed by plotting peak area ratio against concentration, were linear in the ranges of 20–1000 ng ml^{-1} for diltiazem and 0.5–20 µg ml^{-1} for bupivacaine.

After instrumentation, a period of 60 min was allowed for stabilization and for optimization of fluid status. Baseline values were recorded at 10-min intervals for 40 min to confirm the stability of the preparation. Animals were then allocated randomly to three groups.

Group A (bupivacaine group; $n = 7$), received bupivacaine alone, which was given in small, medium and large doses, each consisting of a bolus dose (200, 400 or 600 µg kg^{-1}) followed by an i.v. infusion (25, 100 or 200 µg kg^{-1} min^{-1}, respectively) for 30 min. Haemodynamic variables were recorded at 10-min intervals and arterial blood samples obtained for analysis of plasma concentrations at 20 and 30 min after the start of each dose. Thereafter, bupivacaine was infused at 400 µg kg^{-1} min^{-1} and measurements were made every 10 min for approximately 30 min, until death supervened.

Group B (diltiazem group; $n = 7$), received diltiazem alone, which was given in a bolus dose of 400 µg kg^{-1} followed by a continuous infusion of 12 µg kg^{-1} min^{-1}. Haemodynamic variables were recorded every 10 min for 180 min and arterial blood samples obtained for analysis of plasma concentrations at 30 and 40 min, and then every 20 and 30 min thereafter to correspond to the sampling times in group A.

Group C (diltiazem plus bupivacaine; $n = 7$), received diltiazem as described for group B. After 40 min, and in the presence of continued diltiazem infusion, the procedure for bupivacaine administration, blood sampling and haemodynamic measurements used for group A subjects was repeated.

Statistical analysis

Data are reported as means (SEM). Within-group comparisons were made by analysis of variance for repeated measures followed by the Wilcoxon matched-pairs signed rank test for individual comparisons. These comparisons were applied to baseline values and values obtained during infusion of the three concentrations of bupivacaine in group A; to baseline and each of the diltiazem values in group B; and to diltiazem values and those obtained during only the first two concentrations (because of death-induced reductions in the sample size) of bupivacaine infusion in group C. Between-group comparisons, estimated by the Mann–Whitney *U* test, were limited to baseline values and to time points equivalent to the first two concentrations of bupivacaine administered for the same reason. Pharmacokinetic data were subjected to one-way analysis of variance followed by the Wilcoxon matched-pairs signed rank test for individual comparisons. $P < 0.05$ was considered statistically significant.

RESULTS

Pharmacokinetics

The bupivacaine administration regimen (loading doses followed by continuous infusion) resulted in the rapid attainment of steady state plasma concentrations at each of the three doses (table I) and plasma concentrations at 20 and 30 min varied by less than 10% for each of the three doses. As the infusion rate of bupivacaine increased in group A, the clearance of bupivacaine increased (table I). When bupivacaine was given in the presence of diltiazem (group C), the plasma concentrations of bupivacaine achieved with the three doses did not differ from those in the absence of diltiazem (table II). However, the co-administration of diltiazem increased the clearance of bupivacaine in the small dose. This increase was maintained during the medium and fast rates of administration of bupivacaine so that clearances for medium and large

TABLE I. *Plasma concentrations and clearance values for bupivacaine and diltiazem (means* (SEM)) *for* n *surviving animals in group A (bupivacaine alone) and group B (diltiazem alone). Bupivacaine was given in three doses in each group: small (200 µg kg^{-1} bolus plus an infusion of 25 µg kg^{-1} min^{-1}), medium (400 µg kg^{-1} bolus plus an infusion of 100 µg kg^{-1} min^{-1}) and large (600 µg kg^{-1} plus an infusion of 200 µg kg^{-1} min^{-1}). These were followed by a continuous infusion of 400 µg kg^{-1} min^{-1} until the death of each animal. Diltiazem was given as a loading dose (400 µg kg^{-1}) plus an infusion of 12 µg kg^{-1} min^{-1}.* ** $P < 0.01$ *compared with bupivacaine small dose*

	Group A (bupivacaine)			Group B (diltiazem)		
		Bupivacaine			Diltiazem	
	n	Plasma concn (mg litre^{-1})	Clearance (ml kg^{-1} min^{-1})	*n*	Plasma concn (µg litre^{-1})	Clearance (ml kg^{-1} min^{-1})
Diltiazem						
30 min	7	0	—			
40 min	7	0	—	5	223 (16)	54.7 (4.5)
Bupivacaine						
Small						
20 min	7	1.13 (0.09)				
30 min	7	1.19 (0.12)	20.3 (1.3)	5	243 (12)	49.8 (5.1)
Medium						
20 min	7	2.79 (0.18)				
30 min	7	3.07 (0.24)	33.2 (2.2)**	5	248 (15)	48.8 (3.1)
Large						
20 min	6	5.97 (0.76)				
30 min	5	5.85 (0.41)	34.2 (3.5)**	5	275 (21)	44.5 (3.7)
Infusion						
10 min	3	9.18 (1.77)				
20 min	2	11.72				
30 min	2	12.98		5	292 (25)	41.9 (3.5)
Concn at death	7	12.65 (1.5)		5	No deaths	

TABLE II. *Plasma concentrations and clearance values for bupivacaine and diltiazem given in combination (group C) (means* (SEM)) *for* n *surviving animals in group C (diltiazem plus bupivacaine). Diltiazem was given as a loading dose of 400 µg kg^{-1} followed by a continuous infusion of 12 µg kg^{-1} min^{-1} throughout the procedure. Bupivacaine was given in three doses as in group A (see table I). Diltiazem plasma concentrations in the presence (group C) and absence (group B) of bupivacaine administration were not significantly different.* ** $P < 0.01$ *compared with same values in group A (table I)*

	Group C (bupivacaine plus diltiazem)				
		Bupivacaine		Diltiazem	
	n	Plasma concn (mg litre^{-1})	Clearance (ml kg^{-1} min^{-1})	Plasma concn (µg litre^{-1})	Clearance (ml kg^{-1} min^{-1})
Diltiazem					
30 min	7	0		247 (12)	
40 min	7	0	—	245 (22)	50.5 (4.4)
Bupivacaine					
Small					
20 min	7	0.86 (0.08)		212 (20)	
30 min	7	0.99 (0.11)	29.4 (3.8)**	221 (16)	58.0 (7.0)
Medium					
20 min	7	2.68 (0.27)		264 (25)	
30 min	5	2.66 (0.18)	38.1 (3.3)	260 (36)	48.9 (8.1)
Large					
20 min	4	6.2 (0.26)		344 (43)	
30 min	2	7.48	30.4 (3.1)	410	34.7 (4.7)
Concn at death	7	7.14 (0.67)**			

doses of bupivacaine were similar in the absence and presence of diltiazem.

Plasma concentrations of diltiazem were stable for the 180-min period of administration in group B, indicating that the kinetics of diltiazem did not change significantly during the study (table I). Also, in group C, diltiazem concentrations and clearances were also not altered by the various plasma concentrations of bupivacaine, suggesting that diltiazem elimination was unaltered (table II).

Pharmacodynamics

Baseline values in all groups were similar and no animals were excluded because of haemodynamic instability (tables III–V). In group A animals, bupivacaine produced negative inotropic, chronotropic and dromotropic effects as demonstrated by dose-dependent decreases in SI, CI, LV d*P*/d*t*, %SS and LVSW and increases in LVEDP and paced PR interval (table III). Mean arterial pressure

TABLE III. *Cardiovascular effects of bupivacaine in group A (bupivacaine alone) (means (SEM)) from* n *surviving animals measured after 20 min of infusion of bupivacaine at each dose. HR = heart rate; MAP = mean arterial pressure; LVEDP = LV end-diastolic pressure; %SS = LV segmental shortening; LVSW = LV segmental work; CI = cardiac index; SI = stroke index; SVRI = systemic vascular resistance index; pPR = paced PR interval.* *P < 0.05 *compared with baseline*

		Bupivacaine dose			
	Baseline ($n = 7$)	Small ($n = 7$)	Medium ($n = 7$)	Large ($n = 7$)	Infusion ($n = 3$)
HR (beat min^{-1})	83 (8)	84 (9)	97 (9)	113 (10)*	100 (4)
MAP (mm Hg)	108 (5)	110 (5)	108 (4)	93 (9)	97 (12)
LVEDP (mm Hg)	6.3 (0.7)	7.3 (0.9)	9.4 (0.8)*	13.2 (1.0)*	13.3 (1.4)
LV dP/dt_{max}	1600 (107)	1530 (126)	1215 (82)*	943 (136)*	900 (5)
%SS (%)	10.1 (0.9)	9.2 (0.9)	5.6 (0.8)*	5.8 (0.5)*	4.1 (0.8)
LVSW (arbitrary units)	1.13 (0.13)	0.94 (0.16)	0.57 (0.14)*	0.48 (0.13)*	0.48 (0.16)
CI (litre min^{-1} m^{-2})	3.0 (0.2)	2.9 (0.3)	2.3 (0.1)*	1.8 (0.2)*	1.6 (0.4)
SI (ml min^{-1} m^{-2})	37 (2)	36 (3)	25 (3)*	18 (3)*	16 (3)
SVRI (dyn s cm^{-5} m^{2})	2860 (190)	3070 (310)	3630 (290)	4130 (500)*	5480 (1840)
pPR (ms)	139 (10)	141 (11)	158 (10)	196 (37)*	298 (48)

TABLE IV. *Cardiovascular effects of diltiazem in group B (diltiazem alone) (means (SEM)) from* n *surviving animals measured at the indicated times during administration of diltiazem (group B). For abbreviations, see table III.* *P < 0.05 *compared with baseline*

		Time during administration of diltiazem				
	Baseline ($n = 5$)	40 min ($n = 5$)	70 min ($n = 5$)	100 min ($n = 5$)	130 min ($n = 5$)	160 min ($n = 5$)
HR (beat min^{-1})	115 (11)	104 (9)	103 (9)	108 (7)	102 (8)	99 (10)
MAP (mm Hg)	120 (6)	98 (5)*	94 (5)	96 (5)	89 (6)	90 (14)
LVEDP (mm Hg)	13.6 (1.2)	13.2 (0.8)	14.4 (0.7)	14.4 (1.2)	13.6 (1.0)	14.5 (1.5)
LV dP/dt_{max}	2000 (70)	1880 (107)	1840 (112)	1900 (176)	1560 (75)	1575 (188)
% SS (%)	12.7 (0.7)	11.6 (0.9)	11.4 (0.7)	11.3 (0.4)	10.7 (1.0)	11.0 (0.7)
CI (litre min^{-1} m^{-2})	2.77 (0.20)	2.77 (0.31)	2.83 (0.31)	2.80 (0.32)	2.41 (0.20)	2.13 (0.20)
SI (ml min^{-1} m^{-2})	25.5 (3.6)	26.7 (1.6)	27.7 (2.4)	25.6 (1.9)	23.9 (2.0)	22.0 (2.3)
SVRI (dyn s cm^{-5} m^{2})	3411 (249)	2835 (271)*	2638 (267)	2733 (290)	2858 (247)	3209 (139)
pPR (ms)	156 (15)	201 (17)*	216 (18)	206 (16)	235 (3)	240 (3)

TABLE V. *Cardiovascular effects of bupivacaine and diltiazem in combination (group C) (means (SEM)) from* n *surviving animals measured after 40 min of diltiazem infusion and after 20 min of bupivacaine infusion. No animal survived after the large dose of bupivacaine in this group. For abbreviations, see table III.* P < 0.05: * *compared with baseline in group B (diltiazem alone)*; † *compared with bupivacaine alone (group A) and with diltiazem (group C)*

			Bupivacaine dose		
	Baseline ($n = 7$)	Diltiazem ($n = 7$)	Small ($n = 7$)	Medium ($n = 7$)	Large ($n = 4$)
HR (beat min^{-1})	92 (4)	103 (6)	104 (4)†	104 (6)	92 (12)
MAP (mm Hg)	106 (5)	95 (3)*	93 (2)†	89 (3)†	73 (6)
LVEDP (mm Hg)	4.1 (0.7)	3.6 (0.7)	4.0 (0.7)†	5.9 (0.8)†	8.5 (1.6)
LV dP/dt_{max}	1457 (49)	1414 (111)	1314 (98)	986 (79)	900 (154)
%SS (%)	11.0 (1.2)	10.8 (1.3)	10.1 (1.0)	7.5 (1.1)	6.6 (0.7)
LVSW (arbitrary units)	0.87 (0.18)	0.88 (0.13)	0.80 (0.14)	0.51 (0.06)	0.22 (0.04)
CI (litre min^{-1} m^{-2})	2.6 (0.1)	3.1 (0.2)*	2.8 (0.2)	2.6 (0.2)	1.5 (0.2)
SI (ml min^{-1} m^{-2})	29 (1)	31 (1)	27 (2)	26 (1)	17 (0.2)
SVRI (dyn s cm^{-5} m^{2})	3120 (240)	2330 (110)*	2490 (120)	2630 (190)†	3360 (385)
pPR (ms)	127 (6)	188 (20)*	189 (21)	197 (20)	265 (4)

(MAP) was maintained until plasma concentrations of bupivacaine > 9 mg litre^{-1} were attained because of increases in SVRI in response to the reduction in CI. Thereafter, both SVRI and myocardial contractility decreased, with consequent circulatory failure at a mean plasma concentration of 12.6 (SEM 1.5) mg litre^{-1} (table I).

In group B animals, diltiazem significantly decreased MAP and SVRI from baseline, increased CI but not SI, and prolonged paced PR intervals (table IV). HR and the measured indices of cardiac contractility were unchanged. Cardiovascular alterations then remained constant throughout the 180-min administration period.

In group C, the three doses of bupivacaine had effects on SI, CI, LV dP/dt, %SS and LVSW similar to those in group A animals (table V). An important difference, however, was that in the

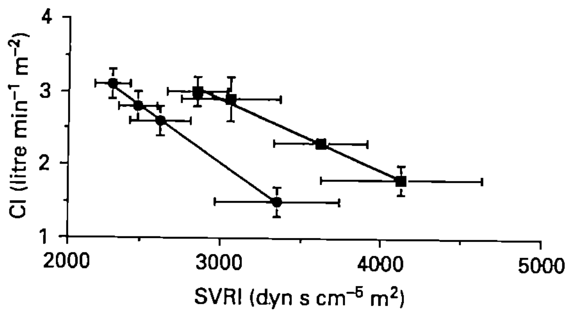

FIG. 1. Relationship between cardiac index (CI) and systemic vascular resistance index (SVRI) during baseline conditions and during the administration of graded doses of bupivacaine in group A (control) (■) and in group C (diltiazem-treated) (●) (means, SEM for five to seven animals in each group). Diltiazem shifted the relationship significantly ($P < 0.05$) to the left which indicates that, at equivalent afterloads, bupivacaine caused a greater depression of CI when given in combination with diltiazem. This suggests that diltiazem enhanced the depressant effect of bupivacaine on cardiac function.

presence of diltiazem, SVRI did not increase to greater than baseline values, with the result that MAP was not maintained. Although the three doses of bupivacaine decreased the measured indices of cardiac contractility in a similar manner in the absence and presence of diltiazem, comparison of the relationships between CI and SVRI (fig. 1) demonstrates that, at equivalent values of SVRI, CI was depressed to a significantly greater extent in the presence of diltiazem. Also, animals in this group were not as responsive to atrial pacing, with all but two animals failing to pace during administration of the greatest dose of bupivacaine. No animals survived beyond this concentration of the drug. The lethal plasma concentration of bupivacaine in the presence of diltiazem (table II) was 7.1 (0.7) mg litre^{-1}. This value was significantly ($P < 0.01$) smaller than in animals treated with bupivacaine alone.

Depression of cardiac conduction and contractility was the predominant cause of death in each group (six of seven in group A and seven of seven in group C). One animal (from group A) died in ventricular fibrillation.

DISCUSSION

In this study we found that the toxicity of bupivacaine was enhanced in the presence of a clinically relevant concentration of diltiazem. Lethal plasma concentrations of bupivacaine were significantly smaller ($P < 0.01$) in the group of animals in which bupivacaine was infused in the presence of diltiazem (7.1 (0.7) mg litre^{-1} *vs* 12.6 (1.5) mg litre^{-1}). Death occurred because of myocardial depression rather than ventricular arrhythmias. The calculated clearance values of diltiazem and bupivacaine were similar given alone and in combination, except for a greater clearance of bupivacaine during infusion of the small dose of bupivacaine in group C.

In group A, bupivacaine *per se*, at a plasma concentration of 2.79 (0.18) mg litre^{-1} decreased LV dP/dt to 75% of baseline with a further decrease to 60% of baseline values at a mean plasma concentration of 5.97 (0.76) mg litre^{-1}. LV %SS, a measure of regional segmental function, was inhibited in a similar manner. These data confirm previous work assessing the effect of bupivacaine on ventricular function [9]. Studies in man are limited, but Scott and co-workers [10], using echocardiographic indices of function, compared ropivacaine with bupivacaine in volunteers and observed depression of cardiac contractility and conduction with bupivacaine plasma concentrations of 1.0–1.5 mg litre^{-1}.

Bupivacaine also prolonged paced PR interval in a dose related manner, with failure to respond to atrial pacing observed at plasma concentrations greater than 9.0 mg litre^{-1} in group A. Significant prolongation of intra-atrial and A–V nodal conduction times has been observed with bupivacaine plasma concentrations as small as 2 mg litre^{-1} [11].

Ventricular arrhythmias are associated with acute bupivacaine toxicity, in both isolated cardiac preparations, intact animals and man [12–14]. Increased concentrations of circulating plasma catecholamines [15, 16] and decreased plasma concentrations of potassium [17] appear to facilitate bupivacaine-induced arrhythmias. Arrhythmias were not the predominant cause of death in our study. This may have been because of the use of fentanyl as an analgesic, and the rigorous maintenance of plasma potassium and bicarbonate within the normal range.

The therapeutic plasma concentration of diltiazem is between 150 and 250 μg litre^{-1} [18] and is similar to that attained in this study. Diltiazem at a mean plasma concentration of 250 μg litre^{-1} had a minimal effect on the measured indices of contractility, but it decreased MAP, SVRI and A–V conduction velocity. Griffin and co-workers [19] also studied the cardiovascular effects of diltiazem infusion in fentanyl-supplemented, anaesthetized dogs. They reported decreases in MAP and SVRI and increases in CI from baseline values at a mean plasma concentration of 363 μg litre^{-1}. Cardiac contractility, as measured by LV dP/dt, was unaltered. With a greater plasma concentration (1483 μg litre^{-1}), LV dP/dt was still unchanged from baseline, while MAP, SVRI and A–V conduction velocity decreased further and CI increased [19]. The increase in CI appeared to parallel the decrease in afterload induced by diltiazem. Skarvan and Priebe [20], found no adverse effects on global right or left ventricular function with diltiazem concentrations equivalent to those achieved in this study. From the foregoing, one can conclude that acute administration of diltiazem in the anaesthetized animal does not alter cardiac contractility.

Adverse interactions of diltiazem with other cardiodepressant drugs (e.g., inhalation anaesthetic agents) have been studied extensively [21–24]. An adverse interaction between lignocaine and diltiazem has also been described [25]; however, that study was performed in dogs anaesthetized with isoflurane, which may have confounded the results. Our study suggests that the negative inotropic and chronotropic effect of large plasma concentrations of bupivacaine is enhanced in the presence of diltiazem. The diltiazem-induced reduction in SVRI was initially protective and preserved CI. However, an abrupt deterioration in contractility and conduction was observed in group C animals with a significantly smaller plasma concentration of bupivacaine than in group A. In the presence of diltiazem, the margin of safety of bupivacaine was reduced approximately two-fold. While direct comparisons between this adverse interaction and that described for verapamil and bupivacaine [4] cannot be made, it appears that small concentrations of bupivacaine may be less hazardous in combination with diltiazem than with verapamil.

Our findings may be explained by a depression of Ca^{2+} fluxes by bupivacaine which result in greater negative inotropy when Ca^{2+} influx has been previously depressed by diltiazem. Alternatively, the observed effects may reflect a pharmacokinetic interaction. Bupivacaine demonstrates concentration-dependent protein binding [26], with free bupivacaine concentrations increasing from 5% of total plasma concentration in the 1–4 mg $litre^{-1}$ range to 50% at concentrations of 12 mg $litre^{-1}$. In addition, diltiazem is subject to displacement *in vitro* by bupivacaine [27]. Although the effect of diltiazem on bupivacaine binding *in vivo* is not known, it is possible that bupivacaine may be displaced by diltiazem. This may explain the sudden deterioration in cardiac function observed in group C and the increase in the clearance of bupivacaine noted during infusion of the small dose of bupivacaine in group C.

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REVIEW ARTICLE

PERIOPERATIVE BLOOD LOSS AND ITS REDUCTION: THE ROLE OF THE ANAESTHETIST

P. SIMPSON

Anaesthesia may influence intraoperative bleeding in several ways, both physiological and pharmacological. Hydrostatic arterial pressure may be altered physiologically by changes in ventilatory pattern, positive end-expiratory pressure (PEEP) and posture, and also by pharmacologically induced alterations in myocardial contractility and peripheral vascular tone. Other factors, such as hypoxia and hypercapnia, may affect vascular diameter, while the use of regional sympathetic block induced by extradural or spinal anaesthesia is also very effective in the reduction of intraoperative blood loss.

Elective hypotension is a specific anaesthetic technique which goes beyond the ability of a good, safe, non stress-inducing anaesthetic to reduce blood loss. Its use may be classified broadly as applicable to situations in which the particular operation would otherwise be impossible (for example cardiovascular or cerebrovascular surgery), situations in which excessive blood loss might be detrimental (for example orthopaedic, spinal and maxillo–facial operations) and situations in which blood loss interferes with surgical visibility or technique (such as middle ear and cosmetic surgery). The demands of elective hypotension in such situations are very different, ranging from acute, short-term "dial-a-pressure" hypotension, to sustained, moderate hypotension for reduction of blood loss. The use of significant hypotension for cosmetic surgery has always been surrounded by controversy, but with modern monitoring techniques, and in the hands of experienced anaesthetists, it is undeniably advantageous and contributes to remarkable results, particularly after injury and trauma. A further controversial topic is the use of hypotension to conserve blood loss in patients in whom the preoperative haemoglobin concentration is reduced or those in whom transfusion is undesirable for various reasons.

The effects of anaesthesia alone and in combination with surgery on blood coagulation and fibrinolysis have been investigated extensively. Although normal coagulation is unaffected by both general and regional anaesthesia, enhancement of fibrinolysis has been demonstrated, particularly in association with extradural techniques.

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KEY WORDS

Anaesthetic techniques, hypotensive. Blood: replacement, reduction. Haemorrhage. Transfusion.

The problem of perioperative deep venous thrombosis and its prevention is also of considerable anaesthetic importance. While the use of extradural anaesthesia to enhance fibrinolysis has been shown to reduce the incidence of deep venous thrombosis, particularly in patients with hip fractures, additional or alternative prophylactic measures are frequently necessary. The influence of such measures on perioperative blood loss and their suitability during operations in which postoperative haematoma formation may produce critical complications is a difficult problem necessitating close liaison between surgeon and anaesthetist, particularly in the high risk patient and those taking oral contraceptive drugs.

Although operative blood loss is dependent primarily upon bleeding from cut vessels, its extent may be influenced in several ways. Bleeding may be arterial, in which case it is related directly to the mean arterial pressure, capillary, when it is dependent upon local flow in the capillary bed, or venous, when it is related to venous return and venous tone and is therefore posturally dependent. Arterial bleeding can be abolished only by the use of a tourniquet, but may be reduced considerably by a reduction in mean arterial pressure or heart rate. Capillary flow is reduced also by elective hypotension and by localized vasoconstriction caused, for example, by infiltration of adrenaline or release of vasoactive amines. Venous tone may be abolished completely by spinal or extradural anaesthesia and by direct acting vasodilators such as sodium nitroprusside.

Although the use of limb tourniquets to produce localized ischaemia during amputation has been practised for centuries, the first use of generalized hypotension to reduce local blood flow was reported by Griffiths and Gillies in 1948 [12]. Their use of "total spinal" anaesthesia to produce pharmacological sympathetic block was followed by Enderby's introduction of ganglion block using pentamethonium in 1950 [8]. In both cases, posture leading to venous pooling enhanced the hypotensive effect. Subsequent techniques have included the use of controlled depression of cardiac output with volatile agents such as halothane [30] and alternative ganglion blocking drugs such as hexamethonium, pentolinium and trimetaphan. More recently, directly acting vasodilators such as sodium nitro-

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prusside [15, 25] and nitroglycerin [1, 16, 42] have been introduced into clinical use. Beta adrenoceptor block and, more recently, combined alpha and beta adrenoceptor antagonism using labetalol are now being used more widely.

PHYSIOLOGICAL FACTORS WHICH REDUCE BLOOD LOSS

Cardiovascular physiology

The most important factor determining the extent of intraoperative haemorrhage is the mean arterial pressure. This is related directly both to cardiac output and to peripheral resistance:

$$\text{Mean arterial pressure} = \text{cardiac output} \times \text{total peripheral resistance}$$

While cardiac output is dependent upon myocardial contractility determining stroke volume and heart rate, peripheral resistance is a function of vascular dilatation:

$$\text{Cardiac output} = \text{stroke volume} \times \text{heart rate}$$

Peripheral vasodilatation is controlled primarily by sympathetic activity, vasodilatation being produced by interruption of sympathetic pathways rather than by any parasympathetic effect. Some cholinergic vasodilator fibres do exist, for example in the smooth muscle of the gut. Hypotension caused by reduction in total peripheral resistance can be achieved, therefore, centrally by drugs such as volatile agents acting on the vasomotor centre, peripherally at the level of the sympathetic ganglia, postganglionic noradrenergic (alpha) terminals, or directly on the blood vessels themselves. It may seem strange that techniques which induce vasodilatation may also reduce bleeding, but it is their effect on mean arterial pressure which effectively reduces local blood flow. In order to produce a measurable effect, local arterial pressure must be approximately 30–40 mm Hg to produce optimal effects and, in addition, venous drainage of the area must be unimpaired.

Effects of posture. Posture influences intraoperative bleeding both by producing regional ischaemia if the operation site is elevated above the level of the heart, and by augmenting the effect of agents such as sympathetic ganglion blocking drugs, by pooling of blood in the dilated venous vascular bed.

The effects of head-up positioning on regional cerebral perfusion pressure in relation to mean arterial pressure at heart level are considerable. For each 2.5 cm of vertical height above the heart, the local arterial pressure is reduced by 2 mm Hg. This is of extreme importance when measuring arterial pressure in the arm while tilting the patient significantly head-up during a period of elective hypotension. While the pressure measured in the arm may be considered adequate for cerebral perfusion, the posture of the patient may make this borderline.

The use of posture to improve the operating field and to reduce bleeding in head and neck surgery is well known. Conversely, operations below heart level, for example those on the lower limb, may be improved by a head-down tilt. However, this is not such an effective way of reducing arterial pressure, as it tends to improve venous return and therefore maintain arterial pressure, in contrast with the head-up position which reduces venous return. Whenever possible, posture should be used to augment pharmacological methods of induced hypotension, particularly those which depend upon venous pooling.

Effect of intermittent positive pressure ventilation (IPPV). Under normal circumstances, venous return to the heart occurs during inspiration when a negative intrathoracic pressure enhances blood flow to the heart, even against the force of gravity. During IPPV, inspiration is associated with positive intrathoracic pressure, inevitably resulting in a reduction in venous return. If such an effect is augmented by posture, the resultant reduction in venous return and therefore cardiac output might be expected to be considerable. Prys-Roberts and colleagues [29] have shown that, in normotensive, anaesthetized subjects, IPPV has little effect on cardiac output, primarily because of the reflex vasoconstriction produced in response to what is effectively a limited Valsalva manoeuvre. In addition, the baroreceptors respond to hypotension by inducing a reflex tachycardia. There are, however, two methods of inducing hypotension in which cardiac output may decline considerably in response to IPPV, as a result of temporary autonomic paralysis. Both ganglion blocking drugs and beta adrenoceptor antagonists may partially or completely block the Valsalva response [3], thus limiting the normal compensatory mechanism.

In general, IPPV is a useful adjunct to any hypotensive technique, largely because it augments pharmacological methods of reducing arterial pressure, thus limiting the dose necessary to produce the desired effect and the postoperative duration of hypotension. In addition, controlled ventilation allows the application of positive end-expiratory pressure (PEEP) to the airway, which is another method of limiting venous return and assisting in arterial pressure reduction. During the inspiratory phase of controlled ventilation, blood flow to the heart is reduced considerably and this therefore occurs predominantly during the passive process of expiration. If PEEP is applied to the airway, both venous return and cardiac output are further reduced.

Respiratory physiology

Effects of carbon dioxide control. Carbon dioxide is a vasodilator and hyperventilation leading to hypocapnia induces vasoconstriction. Hypocapnia can be achieved by moderate hyperventilation. However, care must be taken during hyperventilation with patients in the head-up position, as vasoconstriction may reduce cerebral blood flow to critical values.

Effects of hypotension on pulmonary gas exchange. As pulmonary blood flow is dependent upon gravity, the head-up position leads to a reduction in blood flow to the apical parts of the lung. However, alveolar ventilation occurs throughout the lung, including the upper segments, resulting in considerable ventilation perfusion ($\dot{V}/\dot{Q}$) mismatch and an increase in physiological deadspace. This may be as great as 80% of the tidal volume [7] and is of particular importance in spontaneously breathing patients. The reduction in alveolar ventilation and increased physiological shunt are additional reasons for the use of IPPV during elective hypotension.

In addition, many anaesthetists increase the inspired oxygen concentration during elective hypotension, to minimize the effects of this $\dot{V}/\dot{Q}$ imbalance.

MECHANICAL METHODS OF BLOOD FLOW REDUCTION

Tourniquets

Tourniquets are suitable only for application to limbs or parts of limbs, for example fingers and toes. Their use should be monitored critically for two main features: first, the duration for which the tourniquet is applied, as prolonged ischaemia may result in permanent damage to the limb; second, the pressure applied, as pressure to the tissues underneath the tourniquet may cause necrosis and neurological damage. Measurement of the patient's arterial pressure is essential, so that the tourniquet may be inflated to a pressure sufficiently greater, to occlude the arterial circulation. The pressures commonly used in normotensive patients are 250 mm Hg in the arm and up to 300 mm Hg in the leg. Finger tourniquets are usually applied with pieces of elastic and therefore their pressure is not measured.

It is essential that only correctly designed tourniquet cuffs with a method of pressure measurement and regulation are used, as these incorporate safety devices both to prevent the tourniquet slipping and to prevent accidental deflation. Tourniquet time must be limited to 60 min in the upper limb and 90 min in the lower limb, although ischaemic damage may occur even during these short periods. Tourniquets should not be used in patients suffering from sickle cell disease, as the local acidosis produced may induce sickling as a result of alteration in haemoglobin S.

Local infiltration with sympathomimetic amines

Adrenaline and other related amines are used frequently to induce local vasoconstriction. The concentration of adrenaline should be sufficient to induce vasoconstriction without causing intense or persistent vasospasm which may induce local necrosis. Concentrations of 1:200000–1:400000 are used commonly, similar to those used with local anaesthetics. The total dose of adrenaline should be limited to 500 μg. Accidental intravascular injection of adrenaline may occur during infiltration, and for this reason the use of a volatile anaesthetic with a high arrhythmic threshold, for example isoflurane, is preferable to halothane.

PHARMACOLOGICAL METHODS WHICH REDUCE BLOOD LOSS

Volatile anaesthetic agents

Halothane. Although halothane causes a moderate degree of vasodilatation, the overall reduction in total peripheral resistance is approximately 15–18%. Vasodilatation in the skin and splanchnic vascular beds is balanced by vasoconstriction in skeletal muscle, any additional hypotension caused by halothane being a direct result of myocardial depression. In addition, bradycardia induced by halothane further reduces cardiac output. While halothane is often used successfully in small concentrations as a background to hypotensive anaesthesia, its use as a sole hypotensive agent in larger doses should be discouraged. This is of particular importance in neurosurgery if an increase in intracranial pressure is to be avoided.

Enflurane. The mechanisms and effects of hypotension induced by enflurane are similar to those of halothane. Myocardial depression and vagal stimulation are still significant factors if excessive doses of the drug are used and for this reason it also should be used only in moderate doses, simply as a background agent.

Isoflurane. Unlike both halothane and enflurane, isoflurane has minimal effect on myocardial contractility at low inspired concentrations. The peripheral vasodilator effect is readily adjusted by alterations in inspired concentration. For this reason, it is becoming used increasingly as a hypotensive agent, particularly when only a moderate reduction in arterial pressure is required. It has the additional benefit that increasing doses cause not only vasodilatation and hypotension, but also central nervous depression, thus minimizing any reflex vasoconstriction or tachycardia which may occur as a result of baroreceptor stimulation under relatively light anaesthesia. Isoflurane also appears to have less effect than either halothane or enflurane upon intracranial pressure in patients with normal preoperative values [22]. It has been suggested that, by decreasing afterload, but not simultaneously reducing cardiac output, isoflurane may be detrimental in patients with ischaemic heart disease. This so-called "coronary steal", however, has not been associated with any increase in morbidity or mortality in such patients [36].

Sympathetic ganglionic block

Trimetaphan, pentolinium. These drugs cause autonomic ganglion block by competitive inhibition of acetylcholine. Their effects are not confined to the sympathetic system, as cholinergic transmission also occurs in parasympathetic ganglia. Interruption of sympathetic outflow causes vasodilatation which tends to be relatively slow in onset and recovery. The duration of hypotension induced by trimetaphan is relatively short (10–15 min) and for this reason the drug is often administered by i.v. infusion (3–4 mg min^{-1}). In contrast, a single injection of pentolinium 5–15 mg produces hypotension for about 45 min and allows a slow return of arterial pressure to normal values.

Although several gastrointestinal and urinary symptoms may result from concomitant parasympathetic block, mydriasis and tachycardia are clinically important during induced hypotension. The increase in heart rate which often accompanies hypotension caused by ganglion block may severely impair the effectiveness of these drugs in reducing bleeding. Tachyphylaxis, that is the need for increasing doses of the drug to produce the same effect, is particularly marked with trimetaphan and may make a stable arterial pressure difficult to achieve. Continuous infusion is considerably superior to intermittent bolus dose administration in this respect. Pentolinium is at present unobtainable in the U.K., but may be reintroduced.

Non-depolarizing neuromuscular blocking drugs

Alcuronium, tubocurarine. The use of non-depolarizing neuromuscular blocking drugs to facilitate IPPV as an adjunct to elective hypotension has been advocated for some time. Tubocurarine, the drug used most widely in this situation in the past, and now alcuronium initially were thought to induce a degree of sympathetic ganglionic block. More recently, it has been shown that the main reason for their hypotensive effect is release of histamine, which induces vasodilatation. This far outweighs any effect caused by mild ganglion block.

Alpha adrenoceptor block

Phentolamine, phenoxybenzamine, chlorpromazine, droperidol. Alpha adrenergic blocking agents produce vasodilatation by competitive block of post-synaptic noradrenergic receptors within the sympathetic system. While the effects of phentolamine are relatively short (20–40 min) and easily reversible, those of phenoxybenzamine may last several days as this drug, a nitrogen mustard derivative, forms an irreversible receptor complex. Phentolamine also exerts a myocardial stimulant (beta adrenergic) effect, increasing both oxygen consumption and heart rate. Phenoxybenzamine may cause considerable sedation. While phentolamine 5–10 mg is used in the rapid induction of intraoperative vasodilatation, phenoxybenzamine 0.5–2.0 mg kg^{-1} for 10 days is used more commonly for chronic vascular expansion before surgery, to minimize the effects of circulating catecholamines, for example in the surgical removal of phaeochromocytoma. Both chlorpromazine and droperidol cause mild alpha adrenergic block which is often useful in the preparation of patients before hypotensive anaesthesia or hypothermia.

Beta adrenoceptor block

Propranolol, oxprenolol, labetalol, atenolol, esmolol, practolol. The main advantages of the beta adrenoceptor antagonists for induced hypotension are in the reduction of heart rate and cardiac output. Many anaesthetists believe that the maintenance of a slow heart rate without any additional hypotension considerably reduces operative bleeding. Propranolol has often been used to produce this "rheostatic" hypotension. Although preoperative oral therapy (propranolol 40 mg three times daily) is probably best, propranolol 1–2 mg i.v. may be used during anaesthesia. Beta adrenoceptor block with either propranolol or oxprenolol is used also either before or during operation to counteract the tachycardia produced as a side effect of induced hypotension with either ganglion blocking or direct acting vasodilator drugs. Again, it is best to administer the drugs orally rather than i.v., as this produces a steady intraoperative blood concentration. Although the combined alpha and beta adrenoceptor blocking drug, labetalol, would seem ideal for use in induced hypotension, it is important to realize that the alpha blocking effects of the drug last only for 30 min, compared with a 90-min duration of beta block. In addition, the beta blocking effects are five to seven times as potent as the alpha block. The perioperative use of beta block with either propranolol or labetalol may have considerable benefit in the prevention of wide fluctuations in arterial pressure, particularly in patients with subarachnoid haemorrhage and vasospasm.

Direct acting vasodilators

Sodium nitroprusside. The recent interest in direct acting vasodilator drugs began with the reintroduction into clinical practice of sodium nitroprusside (SNP) [15, 25]. The main advantage of this drug is its evanescent duration of action, allowing rapid reduction of arterial pressure and equally rapid restoration to normal values. It is the only drug capable of predictably producing "dial-a-pressure" hypotension over relatively short periods, for example in the reduction of bleeding during removal of meningiomas and major vascular surgery or to facilitate clipping of cerebral aneurysms. As a vasodilator, SNP inevitably causes an increase in intracranial pressure, and for this reason should not be used during neurosurgery before the skull is open in a patient with increased intracranial pressure. Nevertheless, during induced hypotension with nitroprusside, autoregulation is maintained at cerebral perfusion pressures considerably less than with other drugs [37].

Shortly after the introduction of SNP into clinical practice, reports of fatalities during its use were attributed directly to cyanide poisoning [6, 14, 21]. Each molecule of SNP contains five cyanide radicals which are liberated on breakdown of the drug in either plasma or red blood cells. Several studies, however, have failed to demonstrate significant effects upon red cell oxygen transport by cyanide liberated during the routine clinical use of SNP [4, 41].

The normal metabolic pathway of SNP breakdown is non-enzymatic, occurring in both red cells and plasma (fig. 1). The intracellular reaction is catalysed by the conversion of haemoglobin to methaemoglobin. Ultimately, more than 98% of the cyanide produced from SNP is contained within the red blood cells, while a small proportion is combined with either methaemoglobin or vitamin B_{12}. The majority of cyanide is metabolized in the liver, by the enzyme rhodanase, to thiocyanate which is then excreted in the urine. The rate-limiting factor in cyanide metabolism appears to be the availability of sulphydryl groups and the administration of sodium thiosulphate can considerably enhance thiocyanate production and therefore reduce blood cyanide concentrations [18]. The use of thiosulphate does not appear to affect the hypotension produced by SNP. At the maximum safe doses recommended for

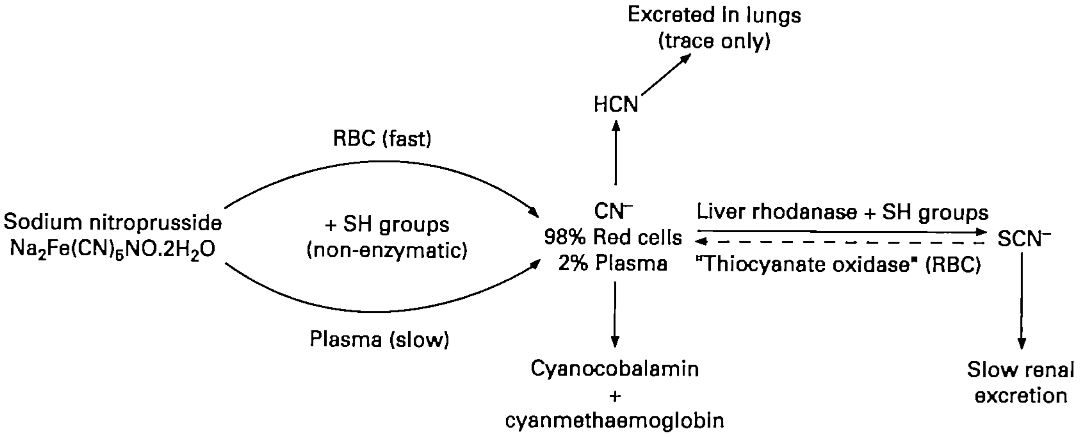
Excreted in lungs (trace only)
HCN
RBC (fast)
Sodium nitroprusside
Na2Fe(CN)6NO.2H2O
+ SH groups (non-enzymatic)
Plasma (slow)
CN⁻
98% Red cells
2% Plasma
Liver rhodanase + SH groups
"Thiocyanate oxidase" (RBC)
SCN⁻
Cyanocobalamin + cyanmethaemoglobin
Slow renal excretion

FIG. 1. Metabolic pathway of sodium nitroprusside. RBC = Red blood cells; HCN = hydrogen cyanide; CN^- = cyanide; SCN^- = thiocyanate; SH = sulphydryl group.

administration of SNP, (1.5 mg kg^{-1} [40] or 10 µg kg^{-1} min^{-1} [38]), small increases in plasma lactate concentration occur which are mirrored by increases in arterial base deficit. These changes are only minor, the maximum base deficit being approximately −6 to −7 mmol $litre^{-1}$, and are reversible spontaneously upon discontinuation of SNP therapy. The routine measurement of acid–base balance during SNP therapy would appear to provide adequate clinical information of the development of cyanide toxicity during routine clinical use.

The use of SNP in patients already anaesthetized with a background hypotensive anaesthetic technique is the method of choice for the production of extreme hypotension for neurosurgery. At present, no other drug provides the predictable and rapid hypotensive effect necessary for many aspects of intracranial surgery. Natural apprehension over the potential toxicity of SNP has centered largely around a few reported cases, all of which were attributable directly to cyanide poisoning [6, 14, 21]. Close examination of these reports confirms that in all cases doses of SNP greatly in excess of those required for routine clinical use were needed to produce toxic symptoms. If the dose of SNP is limited to that already stated above, toxic symptoms do not occur in patients with normal renal and hepatic function. For longer term infusion and in the presence of adequate sulphydryl groups as the substrate for cyanide detoxification by rhodanase, a maximum dose rate of 8 µg kg^{-1} [23] has been shown to be satisfactory.

Trinitroglycerin (*TNG*). Nitroglycerin metabolism involves hepatic breakdown of trinitrate, producing di- and mono-nitrate and finally glycerol. The vasodilator activity of these smaller nitrate molecules is reduced as their size decreases.

TNG produces a steadier and less dramatic reduction in arterial pressure, with a greater effect on systolic than diastolic pressure and tending to maintain blood flow. Recovery from nitroglycerin-induced hypotension is also less rapid, taking between 10 and 20 min, in contrast with the 2–4 min for SNP. It has been suggested that this slower effect of nitroglycerin produces less overshoot of arterial pressure, either at induction of hypotension or after restoration of normal pressure, but as the drug appears less effective in some patients in the production of extreme hypotension, its use may not be ideal in all situations. Although TNG has been advocated as a direct acting vasodilator for neurosurgery, in one study [5], hypotension to 50 mm Hg was not possible in three of 22 patients. Unlike SNP, which dilates both resistance and capacitance vessels equally, TNG exerts its effect principally upon the venous capacitance system. As a result, diastolic pressure is maintained at greater values than with SNP; for this reason TNG maintains coronary artery perfusion more effectively than SNP. While this is probably of little importance in healthy patients, it may be of considerable advantage in patients with impaired myocardial or cerebral circulation. However, the increase in intracranial pressure produced by nitroglycerin may be even greater than with SNP.

Spinal and extradural anaesthesia

Pharmacological sympathectomy using local anaesthetic agents is an effective way of inducing hypotension. Lumbar extradural anaesthesia causes arteriolar dilatation and hypotension, together with a reduction in venous tone. This is enhanced by posturally dependent pooling of venous blood, leading to a decrease in venous return and therefore cardiac output. If the block is extended to the mid-thoracic region, the cardiac sympathetic fibres passing in segments T1–4 are also blocked, preventing compensatory tachycardia which would otherwise occur. This also limits any baroreceptor response, and prevents tachycardia occurring as a result of other pharmacological methods of induced hypotension.

Regional anaesthesia is used most commonly in lower abdominal or pelvic surgery to minimize blood loss, particularly that occurring from the pelvic venous plexuses. The complete abolition of venous tone is extremely effective in minimizing blood loss without the need for profound arteriolar hypotension.

If adrenaline is added to the local anaesthetics used, systemic absorption may partially counteract the hypotensive effect of the regional block. Adrenaline has the advantage of prolonging the effects of the local anaesthetics used, although this can be achieved satisfactorily by the use of intermittent or continuous extradural injections.

MONITORING DURING INDUCED HYPOTENSION

Routine monitoring should include ECG, arterial oxygen saturation, end-tidal carbon dioxide concentration and either direct or indirect arterial pressure measurement, in the knowledge that, assuming a normal intracranial pressure and with the appropriate postural adjustments, the measurement is directly related to cerebral perfusion pressure. In addition, the electrocardiogram provides an indication of the development of relative myocardial ischaemia [33].

Although instruments such as the cerebral function monitor are available for use during hypotensive anaesthesia, their use and, indeed, their possible benefits are relatively limited [28].

Electrocardiographic monitoring

ECG monitoring is essential to demonstrate two vital signs of inadequate myocardial perfusion: the development of ectopic beats and ST segment depression. Although a single-channel ECG is not capable of demonstrating the exact site of any ischaemia, ST segment changes do occur and are usually readily reversible by increasing the arterial pressure. The myocardial response to relative hypoxaemia and hypoperfusion is a sensitive monitor of hypotension being exploited excessively.

Measurement of arterial pressure

Indirect measurement. All these methods involve modifications of the traditional cuff technique and as such are subject to errors in observation and interpretation. Those chiefly used are the oscillotonometer and, more recently, the automated versions of this method, such as the Dinamap. Hutton and Prys-Roberts [13] have shown that errors in interpretation of oscillotonometry have tended to err on the side of safety, as what was originally thought to be systolic arterial pressure has now been demonstrated to represent more closely the mean pressure. The automatic versions are an improvement as they remove the observer bias and, indeed, display not only systolic but also mean and diastolic pressures. All these methods depend upon regular detection of pulsation at the cuff, which is rendered inaccurate by irregular cardiac rhythms such as atrial fibrillation. Moreover, as with all indirect methods of arterial pressure measurement, they are most accurate within the normal ranges of pressure and become increasingly inaccurate at excessively small or large pressures. If hypotension to a systolic pressure of less than 70 mm Hg is anticipated, direct arterial monitoring should be considered essential.

Direct measurement. Although indirect methods of arterial pressure measurement are used during relatively mild hypotensive techniques such as intermittent ventilation with isoflurane, extradural anaesthesia or even, in some cases, the use of ganglion blocking drugs, direct monitoring is an essential part of the technique when vasodilators such as SNP are used and wide variations or rapid changes in arterial pressure are anticipated.

The position of the transducer is the level at which arterial pressure is actually measured and if the mean arterial pressure at head level is desired, the transducer should be placed at this height. Assuming a normal intracranial pressure and with the appropriate postural adjustments, the measurement is then related directly to cerebral perfusion pressure.

Oxygen saturation and end-tidal carbon dioxide monitoring

Induced systemic hypotension inevitably results in a reduction in pulmonary artery pressure and, as pulmonary perfusion is gravity dependent, leads to an increase in $\dot{V}/\dot{Q}$ mismatch within the lung. The ability to monitor respiratory gas exchange non-invasively allows alterations in inspired oxygen and minute volume to be made in specific relation to the patient's needs, rather than on an empirical basis. The inspired oxygen concentration may need to be increased during a period of hypotension to compensate for changes in lung perfusion. In addition, end-tidal carbon dioxide analysis is a sensitive method of detecting air embolism, which may also occur during some cranial or head and neck operations, particularly if PEEP is not used.

PRACTICAL TECHNIQUE OF INDUCED HYPOTENSION

When induced hypotension is superimposed upon a general anaesthetic technique, no single agent is capable of providing the ideal conditions for all operations, the requirements of surgery falling into three broad groups. The first demands relatively slow onset and sustained moderate hypotension with a slow return to normal pressures, and is ideal for most plastic, maxillo-facial and ear, nose and throat surgery when rapid return to normal pressures may cause reactionary haemorrhage. In the second, in which massive blood loss is anticipated, moderate sustained hypotension together with a reduction in heart rate is probably all that is required. In the third group, some operations are not only impossible without profound hypotension, but also require short periods of excessively small pressures, for example during clipping of a cerebral aneurysm. Further indications include resection of aortic coarctation, when rapid fluctuations in arterial pressure necessitating immediate control frequently occur. In general, there is a need for two basic methods of hypotension: elective, slow onset, slow recovery hypotension, or "dial-a-pressure" hypotension.

In all cases of elective hypotension, a background anaesthetic against which hypotension can be induced is essential, the principles of balanced anaesthesia dictating that it is better to use individual agents to achieve specific effects rather than to pursue the toxic properties of an agent such as halothane in the production of hypotension by myocardial depression. An ideal background anaesthetic consists of omission of atropine premedication and the use of generous sedation or analgesia.

Induction of anaesthesia with thiopentone, fentanyl and a long-acting, non-depolarizing neuromuscular blocking drug, for example, alcuronium, should be used. After topical anaesthesia of the larynx, intubation is performed with a non-kinking tracheal tube to remove any possible risk of partial airway obstruction and carbon dioxide retention. Moderate hyperventilation with nitrous oxide and oxygen together with 0.5–1.0% isoflurane provides a background technique against which hypotensive agents can be used.

Under these stable conditions, specific hypotensive drugs may be used with the minimum of side effects such as tachycardia or excessive hypotension. During hypotension, the inspired oxygen concentration may be increased to 40% or even 50% if excessively small pressures are being used over a short period, for example during neurosurgery.

Postoperative management

Recovery staff must be made aware of patients in whom elective hypotension has been used. Not only will they need to monitor arterial pressure accurately and regularly in the recovery room, but they should also continue the anaesthetic management in the same way. Airway care to avoid carbon dioxide retention and partial obstruction is essential, together with frequent recordings of arterial pressure. The patient's position should be determined by the measured arterial pressure, and postural changes may be necessary for several hours to ensure adequate cerebral perfusion. Supplementary oxygen should be administered in all cases until the patient is adequately awake, and may be required for longer where oxygenation is thought to be critical. In patients in whom pharmacological modification of sympathetic responses has been undertaken, such as with the use of ganglion blocking drugs, patients should remain in bed for 12–18 h after operation and, if necessary, lying virtually flat until they are able to sit up without feeling faint.

Contraindications to induced hypotension

Although many anaesthetists are reluctant to use induced hypotension, there are very few patients in whom it cannot be used safely. Most anaesthetists would refrain from utilizing the technique in patients with evidence of severe cardiovascular or cerebrovascular disease, although both these are relative contraindications if, for example, cerebral aneurysm surgery is proposed.

Myocardial ischaemia. This is made worse by an increase in the rate–pressure product. Because hypotensive techniques are designed to reduce both heart rate and arterial pressure, cardiac work is reduced considerably. Many such patients are already receiving beta adrenoceptor blockers and this should be continued during operation. In patients in whom a reduction in afterload is produced by direct acting vasodilators, myocardial work may be further reduced.

Hypertension. Although patients with treated hypertension may be abnormally sensitive to hypotensive drugs, hypotensive techniques may still be used with care. Untreated hypertension, however, is a relative contraindication, as the arterial pressure may be extremely labile and profound hypotension result. It is also important to remember that volatile anaesthetic agents enhance the hypotensive effects of drugs which the patient is already receiving. Monitoring the ECG is essential. Rollason and Hough [32] demonstrated ST depression in hypertensive patients and Simpson, Bellamy and Cole [33] noted similar changes during anaesthesia with nitroprusside-induced hypotension. While the importance of such changes is doubtful, they do demonstrate the need for care when utilizing hypotension in such patients.

Respiratory disease. Limitations in the use of hypotensive anaesthesia in patients with chronic respiratory disease are related to disturbances of normal pulmonary physiology. The increase in physiological deadspace caused by $\dot{V}/\dot{Q}$ imbalance is more important in patients in whom preoperative gas exchange is impaired. Under normal circumstances, hypoxic pulmonary vasoconstriction occurring in poorly ventilated segments of the lung prevents gross disorders of ventilation/perfusion. Vasodilatation induced by direct acting drugs abolishes this response and makes shunting worse.

Reversible airways obstruction and bronchospasm may be made worse by the use of either ganglion blocking drugs or beta adrenoceptor antagonists which are not cardiospecific, and such drugs are contraindicated in asthmatic patients. Increased inflation pressures may lead to carbon dioxide retention and severe hypotension, by impairment of venous return.

Diabetes mellitus. The contraindication to induced hypotension associated with diabetes mellitus is related to the drugs used rather than to the technique. Ganglion blocking drugs, by producing sympathetic block, impair stress-induced gluconeogenesis mediated by adrenaline. Beta blockers may also potentiate hypoglycaemia in insulin-dependent diabetics and it is the combination of hypoglycaemia and hypotension which may produce severe consequences, particularly on cerebral metabolism. Under normal circumstances, however, it is safe to use volatile agents, direct acting vasodilators or local anaesthetic techniques without disturbance of blood sugar concentrations.

Complications of hypotensive anaesthesia

Inadequate hypotension. Although inadequate hypotension is not regarded by many as a complication of hypotensive anaesthesia, failure to appreciate this problem may lead to the excessive use of certain agents and consequent toxic effects. Some patients, for example, with an "overactive" renin–angiotensin system have been shown to be "resistant" to SNP. Before this was appreciated, excessive doses of the drug sometimes were used in the mistaken belief that, eventually, hypotension would be achieved. This led in some cases to SNP toxicity, cyanide poisoning and even death [6, 14, 21]. If hypotension using one drug is not sufficient, then a second agent acting at a different site in the sympathetic system should be used. This has been put to good effect, for example, by combinations of ganglion blocking drugs such as trimetaphan with SNP or, more recently, the combination of isoflurane and SNP.

Excessive hypotension. Moderate hypotension is produced frequently during anaesthesia and many patients are subjected to systolic arterial pressures of 60 mm Hg during routine surgery. It is unlikely that hypotension to this degree, particularly when induced by vasodilatation and accompanied by additional oxygen administration in fit patients, should lead to any permanent adverse effect. Nevertheless, situations have arisen in which permanent damage has resulted from the use of elective hypotension. This is related to excessive hypotension, impaired oxygenation or inadequate arterial pressure monitoring. Lindop [20], surveying the evidence concerning the effects of hypotension on vital organs, stressed the importance of flow rather than pressure in the development of complications. This is particularly important, as normal oxygen extraction by most organs (with the exception of the heart) is only about 25%.

In considering the effects of hypotension on the brain, autoregulation becomes important. It has been shown that the lower limit of autoregulation is better preserved with SNP-induced hypotension than with TNG, flow remaining constant down to mean pressures of 40–50 mm Hg [37]. These data should be interpreted with some caution when extrapolated to humans, because of the effects of anaesthesia and other metabolic derangements upon cerebral blood flow. More detailed studies, such as continuous EEG monitoring [28] and jugular venous oxygen measurements [19], have produced inconclusive results. Probably the most important rule is not to reduce the systolic pressure during operation to less than the diastolic pressure before operation, and to avoid where possible severe head-up tilt unless arterial pressure is being measured at the head level.

The monitoring of ST segment depression to detect myocardial ischaemia would appear to be the most reliable method of demonstrating adverse cardiac effects caused by hypotension [33]. Provided myocardial work is reduced and a compensatory tachycardia produced by hypotension does not occur, severe problems appear to be very rare.

Although those antagonistic to hypotensive anaesthesia may always cite cases of permanent damage or even death related directly to the decreasing of arterial pressure, large series, particularly that collected by Enderby [9], do not bear this out. At East Grinstead, the mortality rate was 1 in 4128 cases of induced hypotension and Kerr [17], in a separate series reported no mortality or morbidity in a series of 700 patients.

EFFECT OF ANAESTHESIA ON COAGULATION AND FIBRINOLYSIS

Several studies have demonstrated that a wide variety of both general and regional anaesthetic techniques have no significant effect on blood coagulation. Thiopentone, diethyl ether, cyclopropane, nitrous oxide, suxamethonium, tubocurarine and halothane have been investigated without detrimental effects [26, 39], as has neuroleptanaesthesia [2, 31].

Enhanced fibrinolytic activity, in contrast, occurs as a direct result of surgery and yet the influence of anaesthesia on the activation of this system is unclear. Engquist and Winther [11] did not find significant anaesthetic-related enhancement of fibrinolytic activity with halothane, cyclopropane, ether, neuroleptic drugs or pentobarbitone, pethidine and nitrous oxide anaesthesia and further studies have confirmed these results for halothane [26] and neuroleptanaesthesia [2, 31]. In contrast, Oyama and colleagues [27] found a significant increase in fibrinolytic activity during enflurane anaesthesia, but this has not been substantiated [34]. Engquist, Askgaard and Funding [10], in a study combining extradural block with general anaesthesia using either halothane alone or a halothane–fentanyl combination, found that increased fibrinolytic activity could be prevented only by a block of sufficient extent to suppress the cortisol response. In a comparative study of general and regional anaesthesia [34], while the use of halothane, enflurane, trichloroethylene or fentanyl, when superimposed on a standardized technique, failed to produce a demonstrable effect, lumbar extradural anaesthesia was associated with significantly enhanced fibrinolytic activity. These findings confirmed those of Modig, Malmberg and Saldeen [24], who demonstrated increased fibrinolytic activity during and after extradural anaesthesia for total hip replacement and suggested that this might be beneficial in the prevention of postoperative deep venous thrombosis. The actual mechanism responsible for the effect of extradural anaesthesia on fibrinolysis is unclear, but it is thought to be related to alterations in regional blood flow as a result of sympathetic block produced by the technique. While overall limb blood flow is increased during extradural anaesthesia, this is almost entirely caused by increased skin blood flow. The concomitant decrease in muscle blood flow, combined with areas of venous stasis, are thought to trigger the fibrinolytic cascade. The protein cascades involved in both coagulation and fibrinolysis are part of the acute phase response to inflammation, but release of all the proteins in this group is not affected significantly by anaesthesia [35].

Prevention of perioperative deep venous thrombosis

Although there are several mechanisms, both mechanical and pharmacological, which may be used to prevent perioperative deep venous thrombosis, many are relatively contraindicated in operations in which blood loss either may be excessive or may interfere with microscopic surgical technique. Full anticoagulation is obviously contraindicated under normal circumstances and many surgeons are wary even of using prophylactic subcutaneous heparin (5000 u., 8- or 12-hourly). Other pharmacological methods such as dextran infusion are similarly unsatisfactory. The recent introduction of the small molecular weight heparins (Fragmin, Clexane) may offer considerable advantage. The small molecular weight heparin–antithrombin III complex avidly binds factor Xa, thereby inhibiting the coagulation cascade. However, unlike conventional heparin, this complex is subject to relatively weak thrombin binding and therefore has little effect on thrombin activity, allowing clot formation to proceed in a normal way. These agents are only marginally more expensive than the currently used "minihep" regimen and need to be administered only once daily. The elective use of lumbar extradural anaesthesia to prevent deep venous thrombosis formation by enhancement of fibrinolysis also is becoming more widely practised, particularly in Scandinavia. In contrast, the use of fibrinolytic activation by streptokinase, anistreplase or alteplase in the presence of established vascular obstruction caused by clot may increase the risk of embolization, although such a situation probably should not arise during routine surgery.

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SHORT COMMUNICATIONS

IN VITRO DISPLACEMENT OF VASOACTIVE MEDIATORS FROM PLASMA PROTEINS: A POSSIBLE MECHANISM FOR PSEUDO-ALLERGIC REACTIONS TO NEUROMUSCULAR BLOCKING DRUGS

W. R. WILLIAMS AND D. J. SHALE

SUMMARY

We have studied the release of prostaglandin $F_{2\alpha}$ *(*$PGF_{2\alpha}$*) and histamine from serum proteins by neuromuscular blocking drugs using equilibrium dialysis, with tracer quantities of radio-labelled mediators as probes. Small concentrations (0.05–0.25 mmol litre*$^{-1}$*) of competitive neuromuscular blocking drugs displaced 16–67% of bound histamine. Greater concentrations of suxamethonium (2 mmol litre*$^{-1}$*) were required for histamine displacement (19%). There was a significant release of* $PGF_{2\alpha}$ *by atracurium 1 mmol litre*$^{-1}$ *and pancuronium 0.69 mmol litre*$^{-1}$*. These findings suggest an alternative mechanism of histamine release by neuromuscular blocking drugs which may be relevant to adverse reactions during use.* (Br. J. Anaesth. 1992; **69**: 508–510)

KEY WORDS

Complications: histamine release, prostaglandin release. Neuromuscular relaxants. Protein: binding.

Adverse reactions to neuromuscular blocking drugs are sometimes categorized as pseudo-allergic because they appear to produce their effect by mechanisms similar to those of the immediate immune response [1]. Histamine has been identified as an important instigator of adverse reactions to neuromuscular blocking drugs and its release has been attributed to the direct action of these drugs on histamine-containing cells [2]. Release of vasoactive mediators from plasma protein in response to neuromuscular blocking drugs has not been considered as an alternative mechanism. This *in vitro* study has investigated the effects of neuromuscular blocking drugs on prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and histamine binding in serum.

METHODS AND RESULTS

Binding of $PGF_{2\alpha}$ and histamine was measured by equilibrium dialysis [3] in serum from healthy volunteers, who were not taking any medication. Tritiated $PGF_{2\alpha}$ 20 µl (0.74 KBq) (6.55 TBq mmol^{-1}; Amersham plc) was added to serum 1.5 ml diluted 1:1 in phosphate buffered saline (PBS). Serum samples in visking tubing were dialysed against an equal volume of PBS containing 0.1% sodium azide for 36 h before the unbound $PGF_{2\alpha}$ was measured in a scintillation counter. To measure histamine binding, tritiated histamine dihydrochloride 20 µl (0.74 KBq) (1.4 TBq mmol^{-1}; New England Nuclear) was added to undiluted serum and dialysed against PBS containing 1% phenol. Neuromuscular blocking drugs were added (in 30 µl of distilled water) to the serum samples before dialysis, although larger volumes of injectable drug preparations were also used. Injectable drug preparations consisted of alcuronium chloride (Roche), pancuronium and vecuronium bromides (Organon Teknika), atracurium besylate and tubocurarine chloride (Calmic). Atracurium besylate, suxamethonium chloride and tubocurarine chloride were also provided as pure agents by Burroughs Wellcome. Pancuronium bromide, histamine dihydrochloride and sodium salicylate were purchased from Sigma Chemical Co. Dorset, England.

Under these experimental conditions, 44.0 (SD 7.3)% ($n = 20$) of the added $PGF_{2\alpha}$ and 13.4 (4.1)% ($n = 20$) of histamine became associated with serum proteins. Atracurium and pancuronium, in final concentrations of 1 and 0.69 mmol litre^{-1}, respectively, inhibited $PGF_{2\alpha}$ binding by > 20% (table I). At this concentration, atracurium had an inhibitory potency similar to that of salicylate. The binding of $PGF_{2\alpha}$ was increased significantly by alcuronium. The neuromuscular blocking drugs were more potent at displacing histamine from plasma protein than at displacing $PGF_{2\alpha}$. With the exception of suxamethonium, at 0.05 mmol litre^{-1} all inhibited histamine binding by > 25%; greater drug concentrations (0.25 mmol litre^{-1}) were more inhibitory. In a concentration of 0.05 mmol litre^{-1}, the histamine releasing effects of both atracurium and tubocurarine were similar to that of "cold" histamine 0.01 mmol litre^{-1}. Greater concentrations of suxamethonium (2 mmol litre^{-1}) displaced 19% of the histamine associated with serum protein, although this effect

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TABLE I. *Changes (%) in the binding of tritiated PGF$_{2\alpha}$ and histamine in the presence of neuromuscular blocking (NMB) drugs, histamine and salicylate in concentrations of 0.05–1.0 mmol litre^{-1}. Pancuronium 0.69 mmol litre^{-1}, suxamethonium 2 mmol litre^{-1} and histamine 0.01 mmol litre^{-1} were also tested. Mean* (SD) *from five to 10 experiments. Significant differences from normal (Student's* t *test)*: $^{*}P < 0.05$; $^{**}P < 0.01$

	PGF$_{2\alpha}$ binding (% change)		Histamine binding (% change)		
	NMB concn (mmol litre^{-1})		NMB concn (mmol litre^{-1})		
	0.2	1.0	0.05	0.25	1.0
Alcuronium	122.1 (7.6)**	105.9 (14.1)	73.2 (15.0)	70.9 (20.0)*	—
Atracurium	96.4 (6.9)	60.8 (3.0)*	45.0 (12.1)*	33.0 (25.6)	—
Pancuronium	97.0 (5.3)	—	72.1 (25.2)	67.1 (28.4)**	—
(0.69 mmol litre^{-1})	—	79.0 (5.2)**	—	—	—
Suxamethonium	106.3 (9.7)	95.8 (3.6)	114.5 (30.2)	—	97.1 (15.3)
(2 mmol litre^{-1})	—	92.6 (13.5)	—	—	80.6 (24.3)
Tubocurarine	108.9 (6.1)	108.7 (11.4)	53.0 (12.1)*	40.4 (17.5)	—
Vecuronium	102.3 (8.5)	83.0 (5.7)	73.4 (21.2)	56.8 (17.0)**	—
Histamine	105.0 (12.2)	105.7 (7.9)	—	—	11.2 (6.4)*
(0.01 mmol litre^{-1})	—	—	52.1 (16.2)*	—	—
Salicylate	86.0 (5.6)**	58.2 (10.8)*	—	—	134.3 (17.7)

was not statistically significant. Salicylate 1 mmol litre^{-1} increased the quantity of histamine associated with serum protein. In contrast, the same concentration of cold histamine displaced nearly 90 % of the radio-labelled histamine.

COMMENT

It is difficult to accept that immediate hypersensitivity is the sole cause of adverse reactions to neuromuscular blocking drugs, because of the small concentrations of specific antibody in reactive patients, the observed cross-reaction to different drugs and the apparent development of immunity with no previous exposure [4]. While there is apparent consensus on the important role of histamine in these adverse reactions, the mechanism of its release remains unknown. The distinction between allergic and pseudo-allergic reactions is more clear with other drugs. Aspirin sensitivity is a more typical pseudo-allergic reaction because of the absence of IgE antibodies in reactive patients. Aspirin and other non-steroidal anti-inflammatory drugs induce adverse reactions through inhibition of cyclo-oxygenase or by their protein binding characteristics, which displace PGF$_{2\alpha}$ from plasma protein [3]. The release of this bronchoconstricting prostaglandin may be relevant to the development of aspirin-induced asthma. As this displacement mechanism may be applicable to pseudo-allergic reactions in general, it was of interest to investigate the potential of neuromuscular blocking drugs for the displacement of PGF$_{2\alpha}$ and histamine from plasma protein.

We demonstrated that small concentrations of neuromuscular blocking drugs can displace radio-labelled histamine from serum protein *in vitro*. The inhibitory effects of these drugs on histamine binding increased with concentration. Furthermore, salicylate and cold histamine showed specificity in inhibiting the binding of radio-labelled PGF$_{2\alpha}$ and of histamine, respectively. Although suxamethonium displaced histamine only at greater concentrations, the displacement mechanism is still relevant to this drug, which is used in clinical practice in concentrations greater than those used for competitive neuromuscular blocking drugs. The concentration of suxamethonium in preparations for injections is 126 mmol litre^{-1} (50 mg ml^{-1}). In contrast, the concentrations of the other tested drugs ranged from 2.7 mmol litre^{-1} (pancuronium: 2 mg litre^{-1}) to 13.0 mmol litre^{-1} (tubocurarine: 10 mg ml^{-1}).

PGF$_{2\alpha}$ binds to plasma albumin, a protein with many low affinity binding sites for drugs and endogenous substances, including histamine. The large plasma concentration of albumin gives this protein a binding capacity that is not readily saturated. Almost all (approximately 99 %) PGF$_{2\alpha}$ in plasma, of the order of 100 pg ml^{-1}, is protein-bound [3]. Knowledge about histamine binding to plasma proteins in normal subjects is limited. A peptide responsible for binding histamine dissociates from albumin during coagulation or enzymic digestion [5]. Although the basic quarternary amine structure of neuromuscular blocking drugs should promote their binding to alpha$_1$-acid glycoprotein (AAG), both alcuronium and gallamine are bound predominantly by plasma albumin [6]. However, increased resistance to the action of atracurium in patients may be associated with an increase in AAG concentration. The binding characteristics of albumin and AAG may form a natural protective mechanism which reduces the effects of released vasoactive mediators. The presence of these protein-bound mediators may not become evident unless they are displaced by increased drug concentrations associated with i.v. injection. Our results provide some support for this hypothesis and suggest that the displacement mechanism may be relevant in a proportion of adverse reactions to neuromuscular blocking drugs.

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ONSET AND RECOVERY OF ROCURONIUM (ORG 9426) AND VECURONIUM UNDER ENFLURANE ANAESTHESIA

M. MAYER, A. DOENICKE, A. HOFMANN AND K. PETER

SUMMARY

We have studied the onset, duration of action and recovery index of twice the ED_{90} of rocuronium (Org 9426) (0.6 mg kg^{-1}) and of vecuronium (0.08 mg kg^{-1}) in patients during enflurane anaesthesia. Rocuronium had a significantly shorter mean onset time of 1.8 (SD 0.4) min, compared with vecuronium 3.4 (0.8) min. Clinical duration (time for the first twitch in the train-of-four to recover to 25% of control) was similar for both drugs (29 (10) min vs 31 (12) min). Spontaneous recovery times (TOF ratio 70%) did not differ significantly between rocuronium (47 (10) min) and vecuronium (44 (11) min). (Br. J. Anaesth. 1992; **69**: 511–512)

KEY WORDS

Neuromuscular relaxants: rocuronium (Org 9426), vecuronium.

Rocuronium (Org 9426) is a new, non-depolarizing neuromuscular blocking agent with a chemical structure derived from that of vecuronium. Results from a previous study using the ED_{90} and three times this dose [1] prompted us to compare the onset time, intubating conditions, clinical duration of action and spontaneous recovery of twice the ED_{90} of rocuronium and of vecuronium under normal clinical conditions. We used rocuronium in a dose of $2 \times ED_{90}$ because in the above study $1 \times ED_{90}$ did not provide adequate intubating conditions and $3 \times ED_{90}$ considerably prolonged its clinical duration.

METHODS AND RESULTS

We studied 24 patients (18–65 y), ASA I or II, undergoing elective surgery, in an open, randomized, prospective study approved by the University's Ethics Committee. All patients gave written informed consent.

Patients with abnormal liver or kidney function, and those receiving drugs which might interfere with neuromuscular blocking drugs, were excluded from the study. Patients were allocated randomly to two groups of 12 subjects each (groups 1 and 2). All patients were premedicated with lormetazepam 2 mg orally approximately 1 h before induction. Anaesthesia was induced with midazolam 0.07 mg kg^{-1} and etomidate 0.3 mg kg^{-1} and maintained with 0.6–1.5 vol % enflurane (end-tidal) and 67 % nitrous oxide in oxygen; supplements of fentanyl 0.05–0.1 mg were given when needed. Ventilation was controlled to maintain normocapnia as assessed by end-tidal carbon dioxide measurement (end-expiratory P_{CO_2} 4–4.5 kPa).

Neuromuscular block was assessed by stimulating the ulnar nerve with supramaximal 2-Hz trains-of-four (TOF) every 20 s and recording the evoked compound electromyogram (EMG) of the hypothenar muscles using a Datex relaxograph.

After 5 min ventilation with 1.5 % enflurane, group 1 received rocuronium 0.6 mg kg^{-1} and group 2 received vecuronium 0.08 mg kg^{-1} into a fast flowing i.v. infusion. Tracheal intubation was performed when the neuromuscular block exceeded 90 %. The following variables of neuromuscular function were obtained from twitch recording: onset time (time from end of injection to maximal effect or $T1 = 0$), abolition of the first twitch of the train-of-four, clinical duration ($T1_{25}$ = time from end of injection to 25 % recovery of T1), $T1_{75}$ (T1 recovery to 75 % of control), recovery index (T1 recovery from 25 % to 75 %) and spontaneous recovery of TOF ratio to 70 % (TOF_{70}). Neuromuscular block was not antagonized in any patient.

Normal distribution was assessed with the Pearson–Stephens test and comparisons between the groups were made by Student's t test for unpaired data. $P < 0.05$ was considered significant.

There were no statistical differences in patient characteristics between the two groups. Onset time after administration of rocuronium was significantly shorter than after injection of vecuronium at a similar degree of maximal neuromuscular block

TABLE I. *Time course of action and recovery after rocuronium 0.6 mg kg^{-1} and vecuronium 0.08 mg kg^{-1} (mean (SD)). *$P < 0.05$ between groups*

	Rocuronium 0.6 mg kg^{-1} ($n = 12$)		Vecuronium 0.08 mg kg^{-1} ($n = 12$)
Onset time (min)	1.8 (0.4)	*	3.4 (0.8)
Maximum block (%)	97 (3)		94 (6)
Clinical duration (min)	29 (10)		31 (12)
$T1_{75}$ (min)	38 (10)		39 (12)
TOF_{70} (min)	47 (10)		44 (11)
Recovery index (min)	10 (3)		9 (3)

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($P < 0.05$). Clinical duration and recovery index did not differ significantly between the two groups (table I). Tracheal intubation was performed after 1.8 (SD 0.5) min in the rocuronium group and 3.5 (0.4) min in the vecuronium group.

COMMENT

Arterial pressure and heart rate did not differ after administration of the two agents, confirming the haemodynamic stability reported in the literature [2–4].

Twice the ED_{90} of each neuromuscular blocker was administered and provided good to excellent intubating conditions. Intubation was achieved in all patients at 90 % block or more. Only a few patients in both groups exhibited slight coughing.

Onset time to neuromuscular block after rocuronium 0.6 mg kg^{-1} was significantly shorter than after a comparable dose of vecuronium (0.08 mg kg^{-1}). The rocuronium onset time of 1.8 min, which was nearly twice as fast as that of vecuronium, is consistent with data from other studies [2, 3, 5]. Increasing the initial dose of vecuronium does not lead to a substantially shorter onset [4], whereas the onset time after administration of three times the ED_{90} of rocuronium (0.9 mg kg^{-1}) was reduced to 70 s [1]. This represents the main advantage of rocuronium over vecuronium.

Rocuronium possesses a relatively small neuromuscular blocking potency compared with vecuronium [2]. Therefore administration of a larger dose of rocuronium, by producing a greater concentration gradient and a greater free plasma concentration, may account for the shorter onset time [6]. The reason why vecuronium did not behave similarly is not clear.

Clinical duration and spontaneous recovery of the TOF ratio to 70 % were similar in both groups. This indicates that rocuronium, given in twice the ED_{90}, is a neuromuscular blocking drug with an intermediate duration of action, similar to vecuronium [3, 5]. Enflurane may potentiate neuromuscular block [5], but it would have affected the two drugs equally. In our study, however, during enflurane anaesthesia the recovery differed only slightly from results obtained during balanced anaesthesia [3, 5].

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CASE REPORTS

PLASMA LIGNOCAINE CONCENTRATIONS ASSOCIATED WITH EXTRADURAL ANALGESIA IN PATIENTS WITH AND WITHOUT MULTIPLE ORGAN FAILURE

C. PUTENSEN, W. LINGNAU, G. PUTENSEN-HIMMER AND M. HEROLD

SUMMARY

We have measured plasma concentrations of lignocaine after thoracic extradural analgesia with continuous infusion of lignocaine in eight intensive care patients with chest wall trauma or after major upper abdominal surgery. Four patients developed multiple organ failure (MOF). Plasma concentrations of lignocaine in arterial blood were measured 4, 8, 24 and 48 h after a continuous infusion of lignocaine was commenced in the extradural space. Plasma concentrations of lignocaine were greater in all patients with MOF (range 2.7–5.1 μg ml⁻¹) than in patients without MOF (range 0.8–1.2 μg ml⁻¹). Because plasma concentrations in patients with MOF were within the low toxic range, extradural infusion of lignocaine should only be considered in intensive care patients without MOF or when plasma concentrations of lignocaine are monitored. (Br. J. Anaesth. 1992; **69**: 513–516)

KEY WORDS

Anaesthetic techniques: extradural. Anaesthetics, local: lignocaine infusion, plasma concentrations. Intensive care: analgesia, multiple organ failure.

Extradural administration of either local anaesthetics or opioids has been shown to be effective for pain management in patients with thoracic injury [1, 2] and in high risk patients requiring intensive care after upper abdominal surgery [3]. However, these patients may be at risk of developing multiple organ failure (MOF).

Extradural administration of local anaesthetics may be associated with systemic toxic effects [4]. Differences in the plasma concentrations of local anaesthetics may be caused by organ dysfunction [5]; there are no data on the plasma concentrations of local anaesthetics during extradural analgesia in patients developing MOF. We have measured, therefore, plasma concentrations of lignocaine during continuous extradural infusion of lignocaine in patients with and without MOF.

PATIENTS AND METHODS

We have studied patients admitted to our intensive care unit with chest wall trauma or after major upper abdominal surgery. All had required ventilatory support for adequate gas exchange and thoracic extradural analgesia was considered appropriate for pain management. Organ failure was defined as severity grade 2 in the multiple organ failure score originally described by Goris and colleagues [6]. Multiple organ failure was present when at least two-organ failure was present. Sepsis was diagnosed according to the definition of Montgomery and colleagues [7]. Patients were excluded from the study if they had neurological injury, spinal injury, sepsis or coagulopathy.

The study was explained in detail to each patient, and informed consent was obtained for all procedures.

All patients were placed in a lateral decubitus position and a 16-gauge Tuohy needle was introduced in the extradural space at the T5–6 or T6–7 level. A therapeutic dose of 2% lignocaine 10 ml without adrenaline was injected extradurally and an 18-gauge extradural catheter was advanced approximately 4–5 cm into the extradural space. A continuous infusion of 2% lignocaine 0.5–0.6 ml kg^{-1} h^{-1} (1–1.2 mg kg^{-1} h^{-1}) without adrenaline [8, 9] was begun 3–5 min after the test dose had been given. In four patients, an additional extradural infusion of fentanyl 1 μg kg^{-1} h^{-1} [10] was required to achieve adequate analgesia (table I).

Arterial blood samples were collected 4, 8, 24 and 48 h after the continuous infusion of lignocaine was started and their plasma concentrations of lignocaine analysed immediately in duplicate by fluorescence–polarization immunoassay as described previously [11, 12], using commercially available immunoassay kits (Abbot, TDx, Chicago, IL).

CASE REPORTS

Patients with MOF

Patient No. 1. A 52-yr-old male with acute alcohol-related necrotizing pancreatitis underwent lapar-

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TABLE I. *Continuous extradural infusion of lignocaine in patients with and without multiple organ failure (MOF). Organ failure was defined as severity grade 2 in the MOF score described by Goris and colleagues [6] and MOF was deemed present when at least two organs failed*

Patient No.	Sex	Age (yr)	Height (cm)	Weight (kg)	Extradural infusion per hour
MOF					
1	M	52	185	98	2% Lignocaine 5 ml+fentanyl 1 ml
2	M	24	178	92	2% Lignocaine 5 ml+fentanyl 1 ml
3	F	35	165	70	2% Lignocaine 4 ml
4	M	24	182	87	2% Lignocaine 5 ml
Non-MOF					
1	M	21	175	72	2% Lignocaine 4 ml+fentanyl 1 ml
2	F	27	164	62	2% Lignocaine 5 ml
3	F	35	168	60	2% Lignocaine 3 ml+fentanyl 1 ml
4	M	30	178	82	2% Lignocaine 5 ml

otomy for early resection of pancreatic necrosis and drainage with peritoneal lavage. Postoperative ventilatory support with $F\text{I}_{\text{O}_2}$ 0.6 and positive end-expiratory pressure (PEEP) 12 cm H_2O was necessary to achieve adequate gas exchange. Dopamine 3 μg kg^{-1} min^{-1}, and dobutamine 5 μg kg^{-1} min^{-1} were required for cardiovascular support. A continuous extradural infusion of lignocaine (table I) was started on the first day after operation, permitting a reduction in i.v. midazolam from 20 to 10 mg h^{-1} and discontinuation of fentanyl 0.3 mg h^{-1} i.v. Renal failure developed subsequently requiring haemofiltration on the third day after operation.

Patient No. 2. A 24-yr-old male with acute necrotizing pancreatitis underwent laparotomy for early resection of pancreatic necrosis and drainage with peritoneal lavage. Adequate gas exchange was achieved by ventilatory support ($F\text{I}_{\text{O}_2}$ 0.5, PEEP 10 cm H_2O). Adrenaline 0.5 μg kg^{-1} min^{-1} was required. A continuous extradural infusion of lignocaine (table I) was started on the first day after operation, but sedation with midazolam 20 mg h^{-1} i.v. was necessary to allow artificial ventilation.

Patient No. 3. A 35-yr-old female with acute necrotizing pancreatitis underwent laparotomy for drainage with peritoneal lavage. Ventilatory support with $F\text{I}_{\text{O}_2}$ 0.5 and PEEP 10 cm H_2O was required to achieve adequate gas exchange. A continuous extradural infusion of lignocaine (table I) was commenced on the second day, resulting in a reduction of the dose of midazolam from 15 to 7.5 mg h^{-1} i.v., with no need for additional i.v. analgesics. The patient was weaned from artificial ventilation to a continuous positive airway pressure (CPAP) of 8 cm H_2O within 4 days. To maintain diuresis, dopamine was infused at 3 μg kg^{-1} min^{-1}. Before operation there was evidence of impaired liver function (aspartate aminotransferase (ASAT) 44 u litre^{-1}, gamma glutamyl transferase 89 u litre^{-1}) which worsened steadily, resulting in hepatic failure (ASAT 124 u litre^{-1}, bilirubin 7.4 mg dl^{-1}) on the third day after operation.

Patient No. 4. A 24-yr-old male with multiple rib fractures, pulmonary contusion, ruptured liver and pelvic fracture underwent laparotomy for haemorrhage. Ventilatory support ($F\text{I}_{\text{O}_2}$ 0.4, PEEP 10 cm H_2O) was required. Diuresis was maintained with dopamine 3 μg kg^{-1} min^{1}. A continuous extradural infusion of lignocaine (table I) was commenced on the second day, resulting in a reduction in the dose of midazolam from 15 to 7.5 mg h^{-1} i.v., without the need for additional i.v. analgesics. The patient was weaned from the ventilator to a CPAP of 6 cm H_2O by the third day. Liver enzyme activity and bilirubin increased steadily, resulting in hepatic failure (ASAT 86 u litre^{-1}, bilirubin 5.9 mg dl^{-1}) on the third day after operation.

Patients without MOF

Patient No. 1. A 21-yr-old male with bilateral multiple rib fractures and pulmonary contusion received ventilatory support ($F\text{I}_{\text{O}_2}$ 0.6, PEEP 12 cm H_2O) to achieve adequate gas exchange. On the second day, a continuous extradural infusion of lignocaine (table I) was started. Subsequently, administration of midazolam was reduced from 20 to 5 mg h^{-1} i.v. and i.v. infusion of fentanyl was discontinued. The patient was weaned from the ventilator to a CPAP of 8 cm H_2O within 4 days.

Patient No. 2. A 27-yr-old female with multiple rib fractures received continuous extradural infusion of lignocaine (table I) immediately after admission. Mask-CPAP of 5 cm H_2O was applied to prevent development of atelectasis.

Patient No. 3. A 35-yr-old female with multiple rib fractures received a continuous extradural infusion of lignocaine (table I) immediately after admission. Mask-CPAP of 5 cm H_2O was applied to prevent development of atelectasis.

Patient No. 4. A 30-yr-old male with multiple rib fractures and pulmonary contusion received ventilatory support ($F\text{I}_{\text{O}_2}$ 0.5, PEEP 10 cm H_2O) to provide adequate gas exchange. A continuous extradural infusion of lignocaine (table I) was started immediately after admission.

RESULTS

There were no adverse local or systemic effects of lignocaine in either the MOF or the non-MOF patients.

We terminated the study because four patients developing MOF had plasma lignocaine concentrations which exceeded the stated lower toxic concentration of 3 μg ml^{-1} [13]. The plasma lignocaine concentrations for patients with and without MOF are shown in table II.

TABLE II. *Plasma concentrations of lignocaine in patients with and without multiple organ failure (MOF). Organ failure was defined as severity grade 2 in the MOF score described by Goris and colleagues [6] and MOF was deemed present when at least two organs failed.* † *Maximal values during the study period*

				Arterial pH			Plasma lignocaine concn (µg ml^{-1})			
Patient No.	Organ failure	ASAT† (u litre^{-1})	Bilirubin† (mg dl^{-1})	Minimal	Maximal	H_2-blocker	8 h	12 h	24 h	48 h
MOF										
1	Lung, circulatory, gastrointestinal, renal	39	3.1	7.33	7.38	Yes	2.7	3.2	2.9	3.1
2	Lung, circulatory, gastrointestinal	45	3.6	7.32	7.37	Yes	3.6	4.4	4.6	4.7
3	Lung, hepatic, gastrointestinal	124	7.4	7.34	7.41	Yes	4.3	4.8	4.6	5.1
4	Lung, hepatic	89	5.9	7.33	7.40	No	3.1	2.9	3.3	3.0
Non-MOF										
1	Lung	29	1.4	7.34	7.40	No	0.7	0.6	0.8	0.6
2	—	22	0.9	7.35	7.43	No	0.9	1.0	1.1	0.9
3	—	27	1.1	7.38	7.44	No	0.7	0.8	0.8	0.7
4	Lung	31	1.3	7.36	7.41	No	0.7	0.9	0.9	1.0

DISCUSSION

We have found that administration of a continuous extradural infusion of 2% lignocaine was associated with toxic plasma concentrations of lignocaine ($\geqslant 3$ µg ml^{-1}) [13] in patients with MOF. In contrast, plasma lignocaine concentrations remained smaller than toxic values in patients without MOF.

The plasma concentration of a local anaesthetic during continuous extradural infusion is determined mainly by absorption into the systemic circulation, its distribution and its rate of clearance by the liver [14]; all of these factors may be altered in the presence of MOF. Body weight and renal disease [5] are reported to have minor effects on the elimination of lignocaine, whereas hypovolaemia [15], cardiovascular disease [16] and hepatic cirrhosis [5] are associated with a decrease in plasma clearance. Clearance of lignocaine is mainly flow dependent [14]. Liver blood flow is determined principally by cardiac output, which in our patients was kept in a higher range (cardiac index > 3.5 litre min^{-1}) to increase oxygen delivery by adequate volume replacement and if necessary by positive inotropic therapy. Thus the presence of either cardiovascular failure or hepatic failure alone may not explain the increased plasma lignocaine concentrations in our MOF patients. Drugs (e.g. H_2-blockers, sedatives) have been shown to decrease both hepatic blood flow and enzyme activity [17] and these factors may also have reduced lignocaine clearance in our MOF patients (table II).

Plasma concentrations of lignocaine in our patients without MOF were slightly smaller than those observed in parturients receiving extradural analgesia with a similar continuous infusion of lignocaine [9]. In contrast, plasma concentrations in our MOF patients were greater than those in patients receiving pain relief with i.v. lignocaine infusions [18]. Despite these concentrations, we did not observe any signs of systemic toxicity in our patients with MOF. The relationship between blood concentrations of local anaesthetic to symptoms of toxicity is less clear [19]. Increased protein binding of local anaesthetics in the presence of increased plasma concentrations of local anaesthetics has been shown to exist without signs of serious toxicity in postoperative patients [20]. Changes in the plasma protein profile of our patients were not measured and so a similar mechanism cannot be excluded. The central nervous system toxicity of lignocaine is sensitive to acid–base balance; all our patients had changes varying between mild acidosis and mild alkalosis (table II). Three of the four MOF patients required additonal i.v. sedation with midazolam that might have masked neurological signs of toxicity.

Although extradural analgesia relieved pain and facilitated weaning from the ventilator, our observations suggest that a continuous extradural infusion of lignocaine should only be considered in intensive care patients without MOF or in the presence of regular monitoring of plasma concentrations of lignocaine.

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ANAESTHESIA FOR CAESAREAN SECTION IN A PATIENT WITH EHLERS–DANLOS SYNDROME TYPE IV

D. BRIGHOUSE AND B. GUARD

SUMMARY

We report the successful use of combined spinal and extradural anaesthesia for elective Caesarean section in a primigravid patient with Ehlers–Danlos type IV (EDS IV). EDS IV is a rare disorder with a high pregnancy-related mortality. Previous reports have not addressed the question of anaesthesia for delivery. It is not possible to be didactic about anaesthetic technique for such patients. The relative risks of general and regional anaesthesia must be discussed fully, and the risks weighed against the wishes of the woman and her partner. (Br. J. Anaesth. 1992; **69**: 517–519)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural, spinal. Complications: Ehlers–Danlos type IV.

Ehlers–Danlos syndrome (EDS) comprises a group of inherited connective tissue disorders. At least nine distinct types have been identified by clinical and biochemical studies [1]. EDS type IV (also described as vascular, ecchymotic or Sack Barabas EDS) has been extensively studied biochemically; it results from abnormalities in metabolism of type III collagen [2]. The gastrointestinal tract, vascular tree and uterus are particularly well endowed with type III collagen, hence the well recognized major complications of spontaneous rupture of bowel, uterus or major vessels in EDS IV [3]. There are several case reports of pregnancy complications in EDS IV, but none address the problems associated with provision of anaesthesia for delivery.

We describe the successful management of delivery in a woman with EDS IV.

CASE REPORT

The patient, a 25-yr-old primigravid, had been diagnosed as severe EDS IV in her early teens. Ion exchange chromatography at that time confirmed that she made virtually no type III collagen, and measurements made in 1982 had showed an increased abdominal aortic compliance—176% of normal. She had received extensive counselling and had been advised against pregnancy. She presented to a local District General Hospital obstetrician at approximately 9 weeks gestation, and was again advised against continuing with the pregnancy. Despite this, she and her husband elected to proceed, and her antenatal care was transferred to the regional obstetric unit for inpatient care at 29 weeks gestation. Her pregnancy had been uncomplicated up to this time.

After multidisciplinary discussion, it was decided that she should remain in hospital until delivery by elective Caesarean section at 36 weeks. The senior consultant vascular surgeon was kept informed of her progress, and was present in the operating theatre for her delivery.

The latter stages of pregnancy were complicated by several episodes of upper abdominal pain, of a nature similar to pain that she had experienced before her pregnancy. This had been thought previously to be associated with spontaneous bleeding into her splenic and hepatic capsules. No definite cause was found for her pain.

During the week before delivery the patient fell and dislocated her right patella. This reduced spontaneously and was treated by the orthopaedic surgeons with a full length plaster of Paris back slab.

Routine ultrasonography confirmed good fetal growth during the third trimester. Ultrasonography was performed also, in an attempt to identify any significant aortic aneurysm. No abnormality was detected, although it was not possible to visualize the entire length of the aorta.

Six units of whole blood were kept cross matched continuously throughout the third trimester.

The patient had been visited weekly during her antenatal admission by the consultant obstetric anaesthetist. She expressed a strong desire to remain awake (and accompanied by her husband) during her operative delivery. After prolonged discussion, this was agreed to by the obstetrician and anaesthetist, and plans were made for Caesarean section under combined extradural and spinal anaesthesia. Preoperative investigations, including coagulation screen, were within normal limits, with a haemoglobin concentration of 113 g litre^{-1}.

The patient was premedicated with oral ranitidine and metoclopramide, and transferred to the anaesthetic room. Two large-gauge i.v. cannulae, an antecubital fossa central venous catheter and a radial artery cannula were inserted using local anaesthesia. A fluid preload of crystalloid 1000 ml and colloid solution 500 ml was given during induction of

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regional anaesthesia by Tuohy guided spinal anaesthesia at the L2–3 interspace with a 25-gauge Whitacre spinal needle and 0.5 % heavy bupivacaine 2.8 ml. The patient was in the left lateral position with a wedge to raise her shoulders. An extradural catheter was inserted before the patient was turned onto her right side and a urinary catheter inserted. Fifteen minutes after subarachnoid injection, the patient had a profound motor block and a bilateral sensory block extending from T3 to S5 on testing with ethyl chloride spray. She was transferred to the operating theatre with a wedge under the right hip to minimize aortocaval compression. Head-up tilt (10°) was applied in an attempt to stop blood tracking up into the paracolic gutters. Oxygen was administered via an MC mask throughout surgery. An additional 500 ml of colloid was infused during this time, followed by whole blood 2 u and crystalloid 1000 ml. The i.v. fluids were warmed using a warming coil and water bath.

The patient was delivered of a male infant in excellent condition, with Apgar scores of 9, 10 and 10 at 1, 5 and 10 min, respectively. Subsequent surgery was prolonged because of meticulous care in obtaining haemostasis, and by difficulty in achieving good uterine contraction, despite i.v. administration of syntocinon 10 u at delivery, and a subsequent infusion of syntocinon 50 u in normal saline 500 ml. No further problems were encountered and the patient was transferred to the high dependency area of the delivery suite for postoperative care. Systemic arterial pressure remained within 15 % of baseline values throughout anaesthesia, surgery and the immediate postoperative period. An infusion of ephedrine 60 mg litre^{-1} had been prepared to treat normovolaemic hypotension, but was not required. Total blood loss was estimated to be 1700 ml. Postoperative analgesia was provided by extradural diamorphine in 0.125 % bupivacaine, which is the normal practice in this maternity unit.

Mother and baby progressed well during the puerperium and were discharged home 10 days after delivery. The uterus was well involuted and wound healing appeared to be progressing satisfactorily. Physiotherapy to her leg continued after operation and she was discharged with a knee brace.

DISCUSSION

Previously published literature often fails to distinguish between the different types of EDS. Prognosis and risks of pregnancy vary considerably between different types of the disease. It has been suggested that vaginal delivery may be the method of choice in the milder forms of the disease such as EDS II (mitis) [4]. The risks of uterine rupture associated with increasing gestation and spontaneous, augmented or induced labour in a patient with EDS IV were considered to outweigh the risks of Caesarean section in our patient. This decision was made largely on an intuitive basis because of the paucity of published literature discussing mode of delivery.

Life expectancy in EDS IV is shortened because of the increased risk of bowel or arterial rupture. There is no effective treatment. Pregnancy complications of EDS IV are reported to result in significant mortality, which may be as great as 25 % [5]. Major reported complications include rupture of bowel, aorta, vena cava, uterus, extensive vaginal lacerations and intractable postpartum haemorrhage. Clotting is usually normal; bruising is thought to be related to friable blood vessels. However, clotting factor deficiencies and platelet abnormalities have been described [6,7].

A review of the abnormal obstetric features of 29 women with EDS did not differentiate between types. The review reported Caesarean section in only one of the 29 women, and this was complicated by postpartum hysterectomy for uncontrollable haemorrhage [8]. Another report of pregnancy complications in a patient with EDS IV described two Caesarean deliveries (in the same patient), both complicated by severe haemorrhage [9]. In both of these reports there was no comment on anaesthetic considerations.

In a series of 20 pregnancies occurring in 10 women with EDS IV, five women died of complications associated with pregnancy. Two died after uterine rupture and two after major vascular rupture in the immediate postpartum period [5]. Provision of analgesia or anaesthesia for delivery was not discussed.

Anaesthesia for Caesarean section

The relative risks of regional and general anaesthesia were discussed at length with our patient and her husband. She had been told previously that she had a significant chance of dying during operation, and her greatest fear was of receiving a general anaesthetic and never regaining consciousness. She repeatedly requested regional anaesthesia so that she could see her baby even if she were to die subsequently.

The couple were warned that if a regional technique was used and major arterial rupture occurred she would lose consciousness rapidly and probably die. She was advised also that administration of general anaesthesia might be requested by the obstetricians in the event of operative complications following delivery. Her husband realized that in both cases he would be asked to leave the theatre immediately. These risks were accepted.

The greatest risk of Caesarean section to our patient was thought to be failure to achieve haemostasis. There was also considered to be a significant risk of major vascular rupture secondary to surgical trauma. Risk of major bleeding is often considered a relative contraindication to regional anaesthesia. General anaesthesia is said to offer a more controlled situation, without hypovolaemia being aggravated by profound sympathetic block. Furthermore, the possibility of a bleeding diathesis is also a contraindication to regional anaesthesia [10].

Arterial rupture in EDS IV may occur in response to mild trauma, and sudden increase in arterial pressure should be avoided. Beta block had been recommended for our patient if systolic arterial pressure was sustained greater than 140 mm Hg, or diastolic pressure greater than 85 mm Hg. The unpredictability of the hypertensive responses to tracheal intubation and extubation at Caesarean section were considered significant risks of general anaesthesia [11].

Orthopaedic complications are well described in EDS, including cervical spine disorders [8]. Injury to the cervical spine at intubation was also considered a potential hazard of general anaesthesia.

Vascular access has not previously been discussed. In addition to adequate peripheral venous access, we considered direct arterial and central venous pressure monitoring advisable. Cannulation of all vessels was not difficult, but was complicated by absence of any sensation of the needle and cannula traversing the vessel wall.

Our choice of regional anaesthesia lay between extradural, spinal or combined extradural and spinal anaesthesia. Single-shot spinal anaesthesia minimizes the risks of bleeding within the extradural space; however, the finite duration of anaesthesia precludes its use in prolonged surgery, and it was therefore considered inappropriate for a procedure in which difficulties with haemostasis might extend the normal duration of Caesarean section considerably.

Extradural anaesthesia permits continuation of sensory block for as long as necessary, and also involves less haemodynamic disturbance than subarachnoid anaesthesia. It gives the opportunity for continuing analgesia into the postoperative period. However, it is recognized that the quality of anaesthesia is inferior to that obtained with subarachnoid block. It may therefore be considered less suitable in situations in which extensive intra-abdominal manipulation is anticipated.

Combined extradural and spinal anaesthesia offers the advantages of subarachnoid block and the flexibility of extradural block [12]. It is the regional technique of choice for Caesarean section in our unit. Our usual technique was modified by the use of additional i.v. access and invasive pressure monitoring. Continuous intra-arterial pressure monitoring allowed rapid correction of any hypotension occurring during institution of anaesthesia, or resulting from intraoperative blood loss. Operative losses in excess of 600 ml (10% of estimated blood volume) were replaced with whole blood because it was anticipated that total perioperative blood loss would be considerable.

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ABOLITION OF THE EXTRADURAL SIEVE BY ADDITION OF FENTANYL TO EXTRADURAL BUPIVACAINE

B. TEHAN

SUMMARY

A patient is described in whom breakthrough of pain occurred from uterine rupture during effective extradural analgesia, demonstrating the hypothesis of the "extradural sieve". Subsequent abolition of this pain by addition of fentanyl to bupivacaine 0.25% raises the question whether or not this combination should be avoided in women with a scarred uterus undergoing "trial of labour". (Br. J. Anaesth. 1992; **69**: 520–521)

KEY WORDS

Analgesia: obstetric. Analgesics: fentanyl. Anaesthetic techniques: extradural. Complications: uterine rupture.

Uterine rupture is a complication which may prove disastrous to mother and baby [1]. Patients at particular risk include those who have had a previous Caesarean section and are undergoing "trial of labour". Extradural analgesia was considered contraindicated because of concern that symptoms and signs of rupture may be obscured [2]. Crawford [3] allayed such fears by suggesting that pathological pain tends to break through an effective extradural block. He termed this the "extradural sieve".

CASE REPORT

A 21-yr-old patient, with a previous history of lower segment Caesarean section, presented at term in spontaneous labour. Her previous Caesarean section had been for twins, one of which had presented as a footling breech. Pelvimetry was normal, so a trial of labour was permitted and vaginal delivery expected. Fetal heart rate was monitored from admission, using a cardiotocograph.

Two hours after onset of labour, cervical dilatation was 4 cm and, at the patient's request, an extradural catheter was sited and analgesia produced with 0.25 % bupivacaine 10 ml. Two hours later, because of failure to progress, an infusion of oxytocin 0.12 iu ml^{-1} at 1 ml h^{-1} was commenced, but was stopped after 15 min when the patient developed "scar pain". A top-up with 0.25 % bupivacaine 10 ml was administered, but failed to relieve this pain and therefore the anaesthetic registrar was called.

The patient described her pain as continuous, severe and lower abdominal, different in nature from that of her contractions. She was clearly agitated and distressed and, although normotensive, had a tachycardia of 120 beat min^{-1}. Abdominal examination revealed tenderness in the right iliac fossa. There was absence of sensation to pinprick bilaterally to T10 dermatome, indicating an effective block for uterine contraction pain. Cardiotocography and fetal scalp pH revealed no evidence of fetal distress and the liquor was clear. The obstetric opinion was that uterine rupture as a cause of this breakthrough pain was unlikely and labour was to continue. In view of this, 1 h after the previous top-up had failed, analgesia was re-established by the administration of fentanyl 50 μg with 0.25 % bupivacaine 10 ml.

Two hours later the patient's pain returned as before, and was unrelieved by 0.25 % bupivacaine 10 ml. Thirty minutes later, with full dilatation of the cervix, she started pushing. At this point, fetal distress, indicated by persistent severe bradycardia (Type II dips) occurred. Blood-stained liquor and an irregular uterine margin was observed by the midwife. Delivery was therefore expediated using forceps. Before the application of forceps, another top-up with 0.25 % bupivacaine 10 ml was given (1 h after the previous top-up) but this also had failed to provide any analgesia.

A brisk postpartum haemorrhage followed, the patient becoming shocked. At emergency laparotomy, complete rupture of the lower uterine segment scar, with right lateral extension, was found and repaired. The subsequent postoperative course for the mother was uneventful. The baby, weighing 3320 g, had Apgar scores of 1 both at birth and at 5 min and, despite several days undergoing artificial ventilation, died.

DISCUSSION

The features of uterine rupture include severe abdominal pain, the feeling of something giving way, gross slowing or cessation of the fetal heart, cessation of uterine contractions, haematuria if the bladder becomes involved, alteration of uterine shape and hypotension, which may be severe [4].

This patient presented with abdominal pain and tenderness breaking through an effective extradural block, thus providing an example of Crawford's "extradural sieve". Fetal bradycardia was a late feature and was associated with an irregular uterine

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margin. The first stage lasted 9.5 h; the second only 30 min; labour was therefore of normal duration. There was no evidence of disproportion.

Uterine rupture is a recognized risk of oxytocin infusion in a patient with a scarred uterus. It is likely that rupture occurred during this procedure, giving rise to "scar pain".

Carrie [5] suggested the use of small concentrations of local anaesthetics (e.g. 0.25% bupivacaine), as greater concentrations might abolish the sieve. To date, the influence of adding fentanyl to bupivacaine on the extradural sieve is unreported.

In this patient, a top-up with 0.25% bupivacaine to which fentanyl was added abolished the sieve. Subsequent top-ups without fentanyl were ineffective. This raises the question of whether opioids should be added to extradural local anaesthetics during trial of labour in patients with a history of previous Caesarean section.

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APPARATUS

BACTERIAL RETENTION PROPERTIES OF HEAT AND MOISTURE EXCHANGE FILTERS

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SUMMARY

We have examined the properties of six heat and moisture exchange filters (HMEF) to ascertain their resistance to liquid flow and their ability to retain a challenge bacterium, Pseudomonas diminuta, *from aqueous and nebulized suspensions. Only one HMEF, the Pall Ultipor was able to withstand a significantly greater pressure of liquid than that found in clinical practice. However, when breached, the HMEF were unable to prevent transmission of micro-organisms from aqueous suspension. Only the Darex Hydrobac filter failed to meet the manufacturer's claim for filter efficiency for nebulized bacteria, mainly because the filter housing failed under test. When the reduction in bacterial cells after passage of the nebulized* Pseudomonas diminuta *through the HMEFs was analysed statistically, the data showed that the HMEF produced by Pall (Ultipor) and Intersurgical (Filter therm) were superior to those produced by DAR Mediplan (Hygrobac), Intertech (HME 225-2835-800) and Gibeck (Humid-vent).* (Br. J. Anaesth. 1992; **69**: 522–525)

KEY WORDS

Bacteria: filtration. Equipment: heat and moisture exchange filters.

Heat and moisture exchange devices (HME) have been in clinical use for more than 30 years. With no moving parts and requiring no external source of energy, their use as conservers of heat and moisture in breathing systems has considerable attraction. HME provide humidification to the respiratory tract; tests on moisture exchange efficiency have shown humidity values in the range 25–28 mg H_2O/litre of expired air [1–5]. HME reduce peroperative heat loss [5, 6] and postoperative shivering [6]. They are cheaper and more convenient to use than hot water humidifiers and reduce entrainment of water by ventilator tubing and valves; this minimizes damage to equipment and helps to reduce the possibility of ventilator malfunction and its consequent risk to the patient [7].

Early designs of HME had multiple layers of wire gauze mesh or polished metal tubes placed in parallel as the condensation surface, but these had problems of increased resistance to gas flow because of blockages and bacterial colonization. Paper-based condensation surfaces resolved some of these earlier difficulties; their performance was better than their metal counterparts, but the humidity was generally less than that produced by heated humidifiers. A further advance was made with the introduction of devices that used plastic foam impregnated with a hygroscopic substance as the active element. More efficient paper materials have also become available with the result that, currently, the most efficient HME filters use a paper-based surface. The discovery that hydrophobic filter membranes also possess heat and moisture exchange properties [5] has led to further development in this area of work, as they enable moisture retention with the added advantage of efficient bacterial filtration or retention. Efficient microbial filtration may be especially important in the infected or immuno-compromised patient in the intensive care unit and so, subsequently, heat and moisture exchange filters (HMEF), which combine the humidification properties of the HME with the bacterial retention properties of a filter membrane, have been developed. Such devices are designed to protect both patients and ventilators from microbial cross-contamination [8]. Previous comparative studies identified those HME that provided humidification of the respiratory tract, but showed that, at that time, only one was an effective bacterial filter [3, 4]. Since then, several HME have been developed possessing both a filter membrane and a heat and moisture exchange membrane. Unfortunately, no comparative evaluation has been undertaken of these newer products. In-house data from companies provide some information about their performance but, in the majority of cases, it is not possible to use these data to compare different brands of HMEF, particularly for bacterial filtration efficiency. The aim of this study was to compare the bacterial filtration properties of HMEF currently available. We have compared the efficiency of the devices when challenged with airborne bacteria and also investigated their liquid filtration properties and resistance to liquid flow.

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MATERIALS AND METHODS

We have examined six brands of heat and moisture exchange filters: Darex, Hygrobac; Gibeck, Humidvent; Intersurgical, Filta therm; Intertech, HME 225-2835-800; Pall, Ultipor; DAR Mediplan, Hygrobac.

Bacterial aerosol challenge test

Preparation of test culture. Pseudomonas diminuta (NCIB 11091) was used throughout the study. The stock organism was maintained on blood agar plates at 35 °C and recultured regularly to maintain the vigour of the micro-organism. The purity of the culture was confirmed periodically using test strips (API 20E) and microscopical examination.

Bacteria grown on blood agar plates were harvested into tryptone soya broth (TSB) immediately before use. The total bacterial cell count was estimated using a haemocytometer counting chamber and the concentration adjusted to approximately 10^8 organisms ml^{-1} using TSB. The viable count of the suspension was measured, after 10-fold serial dilution with TSB, by surface spread plate techniques onto blood agar plates.

Apparatus and test procedure. The test procedure was based upon the method of Duberstein and Howard [9] (fig. 1). For each test, an aliquot of a suspension of the *Ps. diminuta* test culture (5 ml) was nebulized in a DeVilbiss No. 40 nebulizer using a Medicaid CR 60 nebulizer pump operating at 7 litre min^{-1}. The total flow rate was made up to 25 litre min^{-1} with compressed air, supplied through a 0.45-μm filter. The aerosol thus generated was directed onto the patient side of the test HMEF via stainless steel tubing (i.d. 22 mm; length 1 m). Downstream of the test HMEF, two impingers (Porton AGI-30), each containing sterile water 20 ml, were used to collect bacteria. The experiment was run for 15 min, during which time approximately 1–1.5 ml of the suspension had been nebulized. On completion of the test, the water in the impingers was removed using a sterile syringe and each impinger jet and associated glassware rinsed with another 20-ml aliquot of sterile water. All fluids were then pooled.

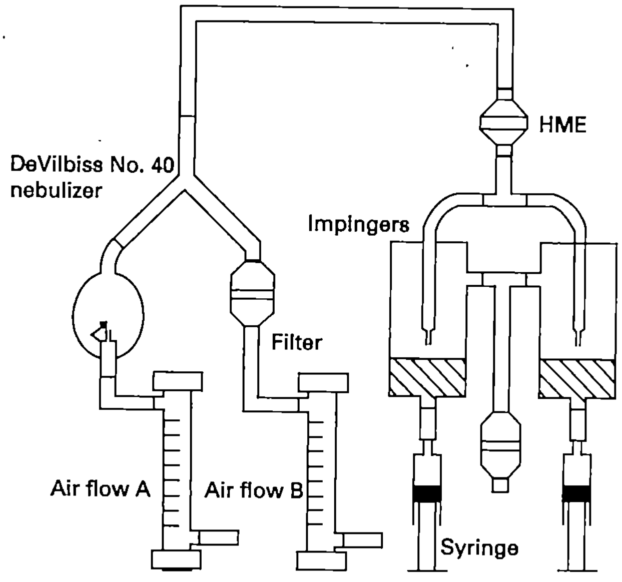

FIG. 1. Test apparatus for aerosol challenge test. Impingers = 12.5 litre min^{-1}; filter = 0.45 μm; airflow A = 7 litre min^{-1}; airflow B = 18 litre min^{-1}.

The viable count of the pooled sample was measured both by serial dilution and by total filtration. A 2-ml aliquot was taken from the final sample and serially diluted as above. The remaining solution was filtered through a 0.22-μm membrane filter and the filter cultured on blood agar plates. All plates were incubated at 35 °C for 2 days.

The apparatus was stripped daily and sterilized by autoclaving. Between tests the components downstream of the test filter were dismantled and disinfected with 70% isopropyl alcohol. All components were rinsed thoroughly with sterile distilled water before reuse.

The efficiency of recovery of organisms from the test rig was established by carrying out several runs ($n = 21$) without a test filter in place. The aerosol size range generated by the nebulizer was established by the use of an Anderson six-stage sampler in place of the impingers.

Where possible, replicate analyses were performed on a minimum of 10 filters and the results analysed statistically using Tukey's test [10].

Liquid bacterial challenge test

A length of 22-mm anaesthetic hose was attached to the patient end of the HMEF, the hose suspended vertically above the filter and 100 ml of the challenge suspension of *Ps. diminuta* introduced into the column. The liquid was allowed to run through the HMEF and was collected in a sterilized glass measure. After 60 min, the total viable counts in both the challenge suspension and the filtrate were measured, after 10-fold serial dilution with TSB, by surface spread plate techniques onto blood agar plates.

Resistance to liquid flow

A length of 22-mm anaesthetic hose was attached to the patient end of the HMEF and the hose suspended vertically above the filter. Water was added slowly to the length of hose until evidence of breakthrough was seen. The height and volume of water above the filter surface at the point of breakthrough was noted.

RESULTS

Aerosol filtration

Using the apparatus without a filter *in situ* established that, over 21 blank runs, an average recovery of only 8.8% of *Ps. diminuta* from the overall challenge was achieved. Losses may be attributed to a number of causes. Many organisms collide with the stainless steel tubing and do not reach the impingers. Also, organisms damaged by the shear force of nebulization or the osmotic shock of collection in the impingers do not survive.

Microbiological test methods are known to show significant biological variability, therefore it was considered necessary to do replicate analyses on at

TABLE I. *Results of aerosol filtration tests for* Ps diminuta. **One of the filters failed under test—data excluded*

Brand	Mean log reduction	Mean filtration efficiency, E	n
Darex, Hygrobac	1.733	95.57	5*
DAR, Hygrobac	5.003	99.9986	10
Gibeck	4.267	99.96	10
Intersurgical	7.704	99.99999	10
Intertech	4.666	99.991	10
Pall Ultipor	7.002	99.9998	10

TABLE II. *Resistance to liquid flow: hydrostatic head required to breach filters (mean of two measurements)*

Brand	Volume (ml)	Height (cm H_2O)
DAR, Hygrobac	107	13
Gibeck, Humidvent	68	10
Intersurgical, Filtration	78	14
Intertech, HMEF 002835	66	14
Pall, Ultipor	450	104

least 10 filters in order to average out these variations. Results from the Anderson samples indicated that 83 % of particles generated were less than 3.3 μm in size.

To enable a comparison of filter performance, it was assumed that the true challenge to the filter would be only 8.8 % of organisms in the total volume of aerosol that was nebulized.

The filtration efficiency, E, was calculated as follows:

$$E = 100 - \frac{100 \times n}{C}$$

where n = total number of viable organisms recovered downstream of the filter and C = challenge to the filter, calculated as follows:

$$C = 0.088 \times N_0 \times V$$

where N_0 = initial concentration of organisms in the challenge suspension (CFU ml^{-1}) and V = volume of suspension nebulized.

Results from the aerosol filtration studies are shown in table I. Each filter is characterized by filtration efficiency. In addition, as the reduction of micro-organisms is over several orders of magnitude, data are presented as log reductions of the challenge after passage of the aerosol through the filters. Filtration efficiencies were generally very good; consequently, the log reductions were analysed statistically and used to compare the performance of the filters. A log reduction of 8 was assumed, when no micro-organisms were recovered during the test, as this corresponded to the minimum detectable log reduction under the experimental conditions.

On the basis of filtration efficiency, the performance of the Darex HMEF was significantly poorer than the five other brands ($P < 0.05$). It should be noted that only five samples of the Darex filter were available for testing. These subsequently proved to be old stock of indeterminate age and history. One of these filters failed under the test conditions. In this instance, the adhesive bond between the filter and the housing parted because of the increased pressure developed during the test, thus allowing bacteria to bypass the filter. Because of the small sample size and the unknown history of the samples, these results were not considered further. The results show, however, that the test method was capable of identifying faulty and poor quality filters. The filtration efficiencies (E) of the other filters were statistically indistinguishable.

With the exception of Darex filters, the design of which has since been altered, all HMEF met their performance specifications for bacterial filtration efficiency, as detailed in the manufacturers' literature.

The log reduction in bacterial numbers proved to be more discriminatory than the filtration efficiency. After statistical analysis using Tukey's test the following could be concluded:

(1) The performance of the Darex filters was significantly worse than that of the five other brands ($P < 0.05$). This confirms the conclusion from the filtration efficiency data; the reasons for this have been discussed above.

(2) There was no significant difference between the DAR, Gibeck and Intertech HMEF ($P > 0.05$).

(3) There was no significant difference between the Intersurgical and Pall HMEF ($P > 0.05$).

(4) The difference in the log reductions for the Pall and Intersurgical brands and the four remaining brands was significant ($P < 0.05$). Therefore the performance of the Pall and Intersurgical filters was superior to that of the DAR, Gibeck and Intertech products.

Resistance to liquid flow

Data on the head of water pressure that HMEF were able to withstand are shown in table II. Because of the variable dead volume of the devices, the results are quoted as both volume of water and height of pressure head. The hydrophobic membrane of the Pall filter had by far the greatest resistance to the flow of water. The results for the other devices were similar to each other.

HMEF vary in materials and construction, with consequent differences in hydrophobic properties, deadspace and surface area. However, because of their small pore size and hydrophobic construction, membrane filters are generally more resistant to liquid penetration than the fibrous felt types. The hydrophobic membrane withstood a pressure greater than that likely to be encountered in the worst clinical situation (> 70 cm). All the other HMEF retained liquid challenges within the range 10–15 cm H_2O, which is equivalent to or slightly greater than the pressure conditions normally found in anaesthetic breathing circuits.

Liquid bacterial filtration

The aerosol challenge test is designed to test the efficiency of the HME filter medium when challenged with dry, individual viable particles. In the clinical situation, it is more normal to find humid conditions and, in many cases, liquid mucus. Therefore liquid filtration properties are sometimes seen as important performance criteria for HME filters.

During this test, the volume of challenge suspension used provided approximately 23 cm of hydrostatic pressure, with slight variations because of the deadspace of individual filter designs. This pressure was sufficient to breach all filters except for the Pall membrane. There was little reduction in the bacterial concentration of the filtrates compared with the challenge suspensions. When the filter element was breached, none of the HMEF was effective as a filter for a liquid suspension of bacteria. However, the head of pressure required to break through the Pall membrane was far in excess of that found in clinical practice. Until this pressure was reached, no liquid and therefore no bacteria may penetrate this filter.

DISCUSSION

The aerosol challenge test used in this paper was designed to test the efficiency of the HME filter medium when exposed to nebulized viable organisms. Under the conditions used, with the exception of one device, all the filters complied with their manufacturer's specifications. No filter is guaranteed to be an absolute barrier and organisms may penetrate it if the challenge is large enough. There is currently no absolute filtration standard for these devices, but clearly the greater the filtration efficiency, the smaller the risk of contamination of the anaesthetic system.

In the clinical situation it is normal for the breathing systems to operate under humid conditions, and in many cases liquid secretions may be present. The liquid challenge and the resistance to flow tests demonstrate that contaminated fluids can soak into and through HMEF at working pressures. Clinically, it has been demonstrated that blood also passes through a filter [11]. Our results show that the hydrophobic filter used in this study continued to act as a barrier to fluids at pressures considerably in excess of those normally encountered in anaesthesia. The question therefore arises as to whether it is clinically preferable to prevent passage of liquid secretions and risk occlusion or to allow the passage of such fluids and risk contamination. There are reports of obstructions attributable to liquid build up [12, 13]; however, the build up of secretions can be monitored through the transparent sides of the devices and potential problems of occlusion or contamination can therefore be averted.

ACKNOWLEDGEMENTS

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ABSTRACTS

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

LEICESTER MEETING

JULY 10–11, 1992

(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

CHANGES IN RESPIRATORY FUNCTION AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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Arterial hypoxaemia occurs after upper abdominal surgery and is most severe on the first two days after operation, but can persist for up to 7 days [1, 2]. Changes in lung volume parallel hypoxaemia as functional residual capacity decreases to less than closing volume and basal airways close [3]. This is associated with pain, hypoventilation and atelectasis. Laparoscopic cholecystectomy avoids the painful incision of open operation, requiring only four 1-cm punctures in the abdominal wall, but opioids may still be required after operation.

After obtaining approval from the Ethics Committee, arterial blood-gas tensions and vital capacity (VC) were measured before operation (day 0) and on the first and fifth days after operation in 19 patients undergoing laparoscopic cholecystectomy and in 11 patients undergoing open operation. The operative method was determined by the surgeon. The groups were comparable in age, smoking history and respiratory function before operation, but there were significantly more females in the laparoscopic cholecystectomy group.

The results indicated a significant decrease in mean Pa_{O_2} from 12.57 to 10.08 kPa on day 1 in the laparoscopic cholecystectomy group ($P < 0.01$) and from 11.38 to 8.84 kPa in the open operation group ($P < 0.01$). The difference between the groups was significant ($P < 0.05$). On day 5, Pa_{O_2} increased to 13.74 kPa ($P < 0.01$) in the laparoscopic cholecystectomy group and to 11.25 kPa ($P < 0.01$) in the open operation group. The difference between the groups was also significant ($P < 0.01$). Changes in VC are shown in table I. The changes from day 0 to day 1 and from day 1 to day 5 were significant in both groups ($P < 0.01$). VC remained less than baseline in the open operation group on day 5 ($P < 0.01$). Pa_{CO_2} did not alter significantly in either group.

In conclusion, both open operation and laparoscopic cholecystectomy cause disturbance in respiratory function, but the latter allowed more rapid recovery in VC.

TABLE I. *Mean* (SD) *changes in vital capacity, expressed as percentage change from day 0, in the laparoscopic cholecystectomy* (*LC*) *and open operation* (*OP*) *groups*

	LC group	OP group
Vital capacity		
Day 1	61.30 (16.8)	40.05 (13.2)
Day 5	97.54 (11.1)	73.86 (16.1)

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EFFECT OF A CERVICAL COLLAR ON THE TIDAL VOLUME OF ANAESTHETIZED ADULT PATIENTS

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Advanced Trauma Life Support (ATLS) procedures are used increasingly to provide a high standard of basic resuscitation of accident victims. Ambulance crews and Accident and Emergency departments are encouraged to suspect the existence of undiagnosed cervical spine injuries [1] and to fit hard, two-piece neck collars onto trauma patients. The effect these have on patients' airways, especially those with decreased consciousness, is unknown. We investigated the effect on tidal volume produced by fitting a "Nec-Loc" collar onto patients with depressed airway reflexes.

Forty adult ASA I patients were studied. Anaesthesia was induced with propofol and maintained with enflurane and 66% nitrous oxide in oxygen via a mask and Mapleson D circuit. Measurements were obtained at the end of surgery whilst anaesthesia was continued with the patient in a supine position on a trolley. One investigator held the mask in place to ensure no leak occurred whilst the other measured tidal volume using a Wright's respirometer. Measurements were made with and without a collar, in random order, first in a neutral position, then using a chin lift (where the chin was gently lifted from below and the mouth opened by pressing down on the bottom lip) and finally using a jaw thrust (where the mandible was displaced forward by pressure behind both angles of the jaw). Both these manoeuvres are recommended by the ATLS course manual for basic airway management [2]. The anaesthetic was discontinued and the patient recovered in the usual manner. Statistical comparison between airway manipulation groups with and without a collar fitted was made using the Kruskal–Wallis and Mann–Whitney tests.

Difficulty was experienced by the investigators in fitting the collar correctly in the first few patients. There were 10 patients in whom airway manoeuvre was impossible after the collar was fitted: five patients had complete airway obstruction when the collar was put on and in four the small collar was too large. There was a significant difference in tidal volumes between the neutral position and both the chin lift and jaw thrust positions in patients without a collar (table II). This suggests that the correct size of collar does not impair tidal volume in patients with depressed airway reflexes but supports the airway in a similar position to that of the basic ATLS manoeuvres.

TABLE II. *Mean* (SD) *tidal volume* (*ml*) *in patients with and without a collar in the neutral, chin lift and jaw thrust positions.* *$P < 0.05$; **$P < 0.01$ *compared with neutral position in patients without a collar*

	Without collar ($n = 40$)	With collar ($n = 40$)
Neutral	264 (196)	272 (216)
Chin lift	367 (247)*	321 (211)
Jaw thrust	403 (235)**	369 (247)

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AUTO-PEEP, LUNG VOLUME AND STERNOTOMY

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I have studied prospectively end-expiratory airway pressure (EEP), a measure of air-trapping or auto-PEEP, in 10 consecutive male patients undergoing coronary bypass surgery (mean age 63 yr (range 52–73 yr)). Spirometry was performed routinely before operation. Anaesthesia was induced with droperidol, midazolam and fentanyl in a dose sufficient to produce apnoea. Ventilation was with nitrous oxide in oxygen: isoflurane was given during extracorporeal circulation.

EEP was measured at four stages during anaesthesia or surgery: before sternotomy, after sternotomy, after extracorporeal circulation and after sternal closure. EEP was obtained during an end-expiratory pause, generated by pressing the appropriate button on the ventilator (Servo 900C). No PEEP was used. One patient, (patient No. 7) had a greatly increased EEP before sternotomy (table III). His FEV_1 was only 50% of the predicted value. After sternal suture, EEP increased in all except one patient ($P = 0.01$, Wilcoxon). Patient Nos 5 and 7 showed particularly large increases in EEP; patient No. 5 had an FEV_1 115% of that predicted.

The changes in EEP were caused by changes in expiratory resistance. Sternotomy causes a mean increase in FRC of 55% during cardiac surgery [1]. After sternal closure, FRC is 16% less than that before operation [1], probably because of increased lung water after extracorporeal circulation and haemodilution. Increased lung water causes an increased airway resistance. There is a quasi-hyperbolic relationship between thoracic gas volume and airway resistance [2] and in some individuals very small reductions in FRC can cause very large increases in expiratory resistance. Sternal closure presumably causes a critical reduction in thoracic cross-sectional area, which in some individuals causes a massive increase in expiratory resistance and EEP.

The study suggests that an increased EEP is common after cardiac surgery. It is associated with increased inspiratory pressures. During surgery, air-trapping can cause the lung to bulge in to the operative area and stretch internal mammary artery grafts. In addition, sternal closure can be difficult. It should be remembered that an increased EEP affects the calculation of compliance.

TABLE III. *End-expiratory pressure (cm H_2O) in patients before sternotomy (I), after sternotomy (II), after extracorporeal circulation (III) and after sternal closure (IV)*

Patient No.	I	II	III	IV
1	1	0	0	2
2	0	2	1	4
3	1	1	1	1
4	0	0	1	5
5	0	0.5	0.5	11
6	2	1	3	7
7	12	1	2	18
8	2	2	0.5	4
9	1	0	0	1
10	0	0.5	1	4

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DETERMINATION OF THE ONSET OF REBREATHING: COMPARISON OF SIX METHODS DURING SPONTANEOUS VENTILATION

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We compared six methods of determining the onset of rebreathing in anaesthetized patients, breathing spontaneously, through an enclosed afferent reservoir (EAR) system. The criteria for rebreathing studied were as follows: (1) the clinical criteria of Kain and Nunn [1]; (2) failure of expired carbon dioxide to return to zero ($F\mathrm{EL}_{CO_2}$), measured at a point 5 cm along the expiratory limb; (3) the detection of carbon dioxide during inspiration at a point 5 cm along the inspiratory limb ($F\mathrm{IL}_{CO_2}$); (4) an increase in functional deadspace ratio ($V\mathrm{D}/V\mathrm{T}$); (5) calculation of the volume of gas rebreathed, expressed as a percentage of $V\mathrm{T}$ ($VR\% V\mathrm{T}$) [2]; (6) inspired carbon dioxide at the mouth of 0.2 kPa $F\mathrm{I}_{CO_2}$ [3].

After Ethics Committee approval, 14 patients, aged 64 to 80 yr and ASA I–III, were studied. Anaesthesia was induced with propofol doses up to 2.5 mg kg^{-1} and maintained with 66% nitrous oxide in oxygen and 1–3% halothane via a laryngeal mask airway (LMA). Fresh gas flow was set initially at 100 ml kg^{-1} min^{-1} and reduced until rebreathing by the Kain and Nunn criteria was seen. Fresh gas flow was then increased to non-rebreathing concentrations.

Respiratory gases were sampled from the connector of the LMA ($F\mathrm{E}'_{CO_2}$). A second sample was taken from 5 cm along the expiratory limb of the circuit in five patients ($F\mathrm{EL}_{CO_2}$) or from 5 cm along the inspiratory limb of the EAR in nine patients ($F\mathrm{IL}_{CO_2}$). These gas samples were analysed for carbon dioxide by separate infra-red analysers (Datex Capnograph). Respiratory flow was measured using a heated pneumotachograph (Fleisch No. 2). All data were recorded on tape via a FM data recorder (Tanberg).

Tidal volume ($V\mathrm{T}$), minute volume ($V\mathrm{E}$), functional anatomical deadspace ($V\mathrm{D}$) (by Fowler's method) and the volume of alveolar gas rebreathed (VR) were calculated by microcomputer. Capnography data were transcribed via a chart recorder (Grass). $VR\% V\mathrm{T}$ and $F\mathrm{IL}_{CO_2}$ were plotted against $V\mathrm{F}/V\mathrm{E}$ and takeoff points determined by arbitrary cubic regression. The points at which the Kain and Nunn, and minimum inspired carbon dioxide criteria were met were noted.

In only two patients did $V\mathrm{D}/V\mathrm{T}$ increase as $V\mathrm{F}/V\mathrm{E}$ decreased, and $F\mathrm{EL}_{CO_2}$ returned to zero in only one patient. Response to other criteria are shown in table IV.

The criteria of Kain and Nunn require a physiological response in the patient and thus are late. $VR\% V\mathrm{T}$ detects the onset of rebreathing before the Kain and Nunn criteria are detected, but it is not feasible for monitoring. $F\mathrm{IL}_{CO_2}$ and $F\mathrm{I}_{CO_2}$ are clinically feasible but offer no advantage over the Kain and Nunn criteria.

TABLE IV. *Mean (SEM)* $V\mathrm{F}/V\mathrm{E}$ *response to the criteria of rebreathing*

	$VR\% V\mathrm{T}$	Kain and Nunn	$F\mathrm{IL}_{CO_2}$	$F\mathrm{I}_{CO_2}$
$V\mathrm{F}/V\mathrm{E}$	0.86	0.60 (0.040)	0.56 (0.035)	0.53 (0.044)

ACKNOWLEDGEMENT

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MOUTH MASK VENTILATION: USE OF A PALL ULTIPOR BREATHING SYSTEM AND EFFECT OF MASK DESIGN

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Mouth mask ventilation can be studied in a clinical setting if

TABLE V. *Mean (SD) minute volume ($\dot{V}_E$), ventilatory frequency (f), tidal volume (V_T) and peak airway pressure (Paw) using the Laerdal pocket mask (LPM) with or without the Pall breathing system filter (PBSF) and the LPM and new mask (NM)*

	V_E (litre)	f (b.p.m.)	V_T (litre)	V_T achieved (b.p.m.)			*Paw* achieved (b.p.m.)			
				V_T (litre)			*Paw* (cm H_2O)			
				< 0.5	0.5–0.8	> 0.8	< 20	20–30	30–40	> 40
LPM	13.7	11.0	1.3	1.5	2.5	7.5	1.0	2.0	6.0	2.5
	(3.5)	(2.5)	(0.4)	(2.3)	(3.3)	(4.5)	(2.5)	(2.0)	(3.5)	(3.1)
LPM+PBSF	13.5	10.6	1.3	1.0	2.0	7.5	1.0	1.5	5.5	3.0
	(3.7)	(2.2)	(0.4)	(3.3)	(3.5)	(4.6)	(3.0)	(2.2)	(3.4)	(3.1)
LPM	13.5	11.0	1.2	1.0	2.0	8.0	1.0	1.0	6.5	2.5
	(4.1)	(2.1)	(0.3)	(2.6)	(2.8)	(4.3)	(2.7)	(1.8)	(3.0)	(2.8)
NM	15.6	11.0	1.4	0.5	2.0	8.0	0.5	1.5	5.5	4.0
	(4.5)	(2.2)	(0.4)	(1.9)	(2.9)	(0.4)	(1.9)	(2.0)	(2.2)	(3.6)

patients are protected from contamination by the resuscitator. This protection could be provided by resuscitators expiring through a Pall breathing system filter attached to the one-way valve of a Laerdal pocket mask. To study the effect of using a Pall breathing system filter in this way, we measured peak airway pressure (*Paw*), tidal (V_T) and minute volume (V_E) and ventilatory frequency during ventilation of a recording mannikin using the Laerdal pocket mask with or without the Pall breathing system filter.

To investigate the possibility that the design of the mask itself would affect the efficiency of mouth mask ventilation, we repeated these measurements during ventilation of the mannikin with the Laerdal mask or with a new mask made from a vital signs, adult, low pressure mask and Laerdal lip valve: a Laerdal oxygen nipple was added to allow oxygen supplementation.

A Laerdal Resusci-Annie recording mannikin was modified by adding a Honeywell pressure transducer to measure *Paw* in the inspiratory limb. An Abbrico spirometer (V_T range and ventilatory frequency) and a Dräger V_E meter (V_T and V_E) were added to the expiratory port. Calibrated signals of *Paw* and V_T were recorded using a commercial software program.

Eighteen anaesthetists (15 males, mean age 31 yr (range 25–36 yr)) and 12 students (eight males, mean age 28 yr (range 20–41 yr)) were asked to ventilate the mannikin at 12 b.p.m. > 800 ml for four 2-min periods with the Laerdal mask with or without the Pall breathing system filter and subsequently with the new or Laerdal mask, in random order (10 litre min^{-1} ventilation). Subjects were asked if they found the Laerdal mask easier to use with or without the Pall breathing system filter and if they found the Laerdal or new mask easier to use.

Paw and V_T recordings were printed and blinded, and breaths were classified into 10-cm H_2O ranges and V_T into < 500 ml, 500–800 ml or > 800 ml. Paired Student's *t* tests were used to determine significant differences in V_T, V_E and ventilatory frequency. Ranges of *Paw* and V_T were compared by Wilcoxon rank sign and subject responses by chi-square goodness of fit ($P < 0.05$).

Eight subjects found the Laerdal pocket mask easier to use with a Pall breathing system filter compared with nine without the Pall breathing filter. Four and 24 subjects found the Laerdal and new mask easier to use, respectively (table V).

The Pall breathing system filter did not affect mouth mask ventilation. The new mask increased V_E and V_T and was easier to use. Although the Laerdal pocket mask is more portable, a self-inflating resuscitator bag can be added to the new mask to allow a change to two-resuscitator bag valve mask ventilation.

COMPONENTS OF THE INSPIRED TO ARTERIAL ISOFLURANE PARTIAL PRESSURE DIFFERENCE

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The relationship between end-expired and arterial partial pressure of inhaled anaesthetic agents is important for both theoretical and practical reasons. In formulating the concept of MAC, the assumption is made that "the alveolar partial pressure is transmitted without change to the arterial blood" [1]. However, recent work on isoflurane [2, 3] has shown mean arterial to end-expired partial pressure ratios of 0.79 and 0.86. It appears that the effects of increased deadspace and shunt, seen in anaesthetized patients, were insufficient to account for all of the observed end-expired to arterial partial pressure gradient for isoflurane. Therefore, we studied the components of the partial pressure gradient for isoflurane between inspired gas and arterial blood.

Six patients, aged 57–79 yr, undergoing major elective vascular surgery were studied. Subjects were ventilated with nitrous oxide in oxygen and 0.52–0.86% isoflurane. Partial pressure of isoflurane was measured using a Datex Capnomac or by gas chromatography in inspired, end-expired and mixed expired gas, and arterial and mixed venous blood. Samples were obtained simultaneously after a period of at least 25 min of anaesthesia at a constant inspired isoflurane concentration, with end-expired isoflurane increasing by not more than 0.02% over the preceding 15 min. Alveolar deadspace dilution of end-expired gas was calculated for carbon dioxide and this dilution factor used to calculate the "ideal" alveolar pressure (P_A). Shunt fraction was calculated for oxygen and then used to calculate the partial pressure of isoflurane in the pulmonary end-capillary blood.

Our results showed that deadspace, in addition to shunt, accounted for only 0.05 kPa (30%) of the total mean end-expired to arterial gradient of 0.17 kPa (SEM 0.01 kPa) (table VI). We suggest that the remaining gradient is a result of diffusion limitation across the alveolus, which will be influenced by rate of uptake into pulmonary capillary blood. This would reduce the partial pressure of isoflurane at the periphery of the alveolus where exchange with blood occurs. This view is supported by the close relation between blood solubility and published $P_A/P_{E'}$ ratios for four agents. This in turn depends on solubility and flow rate.

We obtained a mean arterial:end-expired isoflurane ratio of

TABLE VI. *Components of the inspired to arterial isoflurane partial pressure gradient*

Component	P_A (kPa) (Mean (SEM))	% Inspired	Comment
Inspired	0.69 (0.05)	100%	
End-expired	0.52 (0.05)	75%	Deadspace
Ideal alveolar	0.50 (0.04)	72%	Unexplained gradient
End-capillary	0.38 (0.04)	55%	Shunt
Arterial	0.35 (0.03)	51%	

0.66 (SEM 0.02). We conclude that whilst end-expired isoflurane partial pressure may reflect arterial partial pressure adequately for clinical purposes, end-expired to arterial partial pressure ratios probably differ for different anaesthetics. MAC values may not therefore bear a constant relationship to partial pressures in arterial blood.

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CONTROL OF CARBON DIOXIDE IN CIRCLE SYSTEMS

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Carbon dioxide balance in anaesthetic breathing systems without directional valves has been studied extensively. In circle systems with valves, but without soda lime, it has been established that $P\acute{E}_{CO_2}$ is regulated by fresh gas flow (FGF) during controlled ventilation [1]. The order in which the components of the circle are arranged is important in relation to gas economy in these systems [2].

We studied carbon dioxide balance in clinical practice using three representative circle systems (M & IE Jumbo, Scania and M & IE Exeter). The latter is unusual in permitting rearrangement of components and having directional valves close to the patient. Carbon dioxide was measured continuously using an inline carbon dioxide analyser (H-P47210A), tidal volume (V_T) using an Electronic Wright respiration monitor and minute ventilation ($\dot{V}_E$) with a Mechanical Wright respirometer.

We found that without soda lime, $P\acute{E}_{CO_2}$ was regulated by FGF during controlled ventilation. During spontaneous ventilation, FGF determined whether rebreathing of carbon dioxide occurred but not $P\acute{E}_{CO_2}$. However, if soda lime is not to be used then greater economy in fresh gas can be achieved using valveless systems.

Soda lime in circle systems is highly efficient in removing carbon dioxide and we found that during spontaneous breathing with soda lime in the circle, the breathing system did not affect carbon dioxide balance. If ventilation is controlled, then $P\acute{E}_{CO_2}$ is regulated by $\dot{V}_E$ for a range of ventilatory frequencies, which in our study extended from 10–30 b.p.m. The optimum combination of V_T and ventilatory frequency remains to be determined. Large tidal volumes are generally considered desirable to minimize intra-operative pulmonary collapse but may cause depression of cardiac output and increased $\dot{V}/\dot{Q}$ mismatch. Ventilation which appears adequate causes undesirable hypocapnia and the routine use of added deadspace or a variable shunt around the soda lime may prove desirable for routine clinical use in order to maintain normocarbia.

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A LONGITUDINAL STUDY OF GASTRIC EMPTYING OF A TEST MEAL DURING PREGNANCY

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Differential rates of gastric emptying of solid and liquid phases have been demonstrated [1]. Several studies have examined the gastric emptying of liquids in pregnancy [2, 3], but to date, no studies have examined the rate of gastric emptying of a test meal. The aim of this study was to determine whether any delay exists in the gastric emptying of a test meal in any of the three trimesters of pregnancy compared with after delivery.

After Ethics Committee approval and informed patient consent, the gastric emptying of a test meal in 10 primigravidae was studied prospectively using paracetamol absorption as an indirect measure. All patients were studied at 12–14, 24–26 and 37–38 weeks gestation, and 6 weeks after delivery. No patient was taking iron supplements at the time of study. After ingestion of Vitafood (Boots) 60 g and two crunch and slim bars, three paracetamol tablets (500 mg) were administered with 50 ml of water. Blood samples (10 ml) were withdrawn at 20-min intervals for 2 h and 40 min for analysis of paracetamol concentrations by HPLC. The time to maximum concentration (tC_Pmax), maximum concentration achieved ($C_P$max) and the corresponding area under the curve at 60 (AUC_{60}), 120 (AUC_{120}) and 160 (AUC_{160}) min were determined.

All patients remained well throughout the pregnancy. Mean age (25 yr (range 18–31 yr)), body mass index at booking (23.7 kg m^{-2} (22.2–26.7 kg m^{-2})) and weight gain by 37 weeks (12.3 kg (8.5–18 kg)) were within normal limits. tC_Pmax, $C_P$max and AUC_{60}, AUC_{120} and AUC_{160} were distributed normally and were analysed using MANOVA. There was no statistically significant differences ($P < 0.05$) between these variables (table VII). The power of the study to detect a delay in tC_Pmax of 30 min or more was 0.9.

We conclude that in a group of primagravidae studied throughout the three trimesters of pregnancy and 6 weeks after delivery, a delay in gastric emptying of a test meal was not demonstrated.

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GASTRIC REGURGITATION DURING GENERAL ANAESTHESIA IN THE SUPINE POSITION WITH THE LARYNGEAL AND FACE MASK AIRWAYS

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Regurgitation of gastric contents has been reported to occur in 33% of patients during spontaneous ventilation using the laryngeal mask airway (LMA) [1]. This finding did not accord with our experience and therefore we repeated the study.

Sixty ASA I or II patients undergoing elective body surface surgery in the supine position were allocated randomly into two

TABLE VII. *Mean (SEM) pharmacokinetic variables during the three trimesters of pregnancy and 6 weeks after delivery*

	Gestation (weeks)			6 weeks post-partum
	12–14	24–26	34–36	
tC_Pmax (min)	114 (9)	105 (10)	118 (7)	102 (10)
$C_P$max (μg ml^{-1})	22 (1.8)	21 (1.8)	21 (1.5)	25 (1.6)
AUC_{60} (μg ml^{-1} min^{-1})	84 (25)	138 (58)	82 (24)	154 (47)
AUC_{120} (μg ml^{-1} min^{-1})	526 (83)	608 (95)	472 (57)	732 (70)
AUC_{160} (μg ml^{-1} min^{-1})	875 (85)	937 (104)	828 (55)	1110 (75)

TABLE VIII. *Patient details (mean (SD or range))*

	FMGA group	LMA group
n	30	30
Sex (M/F)	10/20	18/12
Age (yr)	48.8 (21–60)	46.8 (20–60)
Weight (kg)	71.1 (10.2)	72.6 (15.3)
Surgery (min)	42.0 (13.7)	40.1 (17.1)
Regurgitation	Nil	Nil

groups of 30. Any patient with symptoms of, or receiving treatment for, gastro-oesophageal disease was excluded. The anaesthetic technique was standardized and comprised premedication with temazepam 10–20 mg, induction with propofol 2–3 mg kg^{-1} and maintenance with 1–2% isoflurane and nitrous oxide in oxygen delivered through either a laryngeal mask airway (LMA) or face mask plus Guedel airway (FMGA). Increments of fentanyl 25 μg were given when required. Ten minutes before induction of anaesthesia, a methylene blue capsule (75 mg) was swallowed in the sitting position with 20 ml of water. At the end of surgery, the oropharynx was inspected for blueish discolouration which was taken to be a sign of gastric regurgitation.

There were no differences between the patient groups apart from sex ratio (table VIII). Furthermore, signs of regurgitation were not observed in either group. However, two patients not included in the analysis had signs of regurgitation after vigorous coughing during light LMA anaesthesia. Airway suction was performed without complications. A similar case has been reported [2].

Compared with a previous report [1], there is no apparent explanation for the absence of regurgitation in our patients. The onset of dissolution of the methylene blue capsule varied from 0.5 (pH 6.2) to 10 min (pH 1.0). We used isoflurane (rather than halothane) but we are unaware of any differing actions between the two agents on the oesophageal and gastric musculature.

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A LOGISTIC REGRESSION MODEL FOR RISK STRATIFICATION OF FIXED PATIENT FACTORS FOR POSTOPERATIVE EMESIS

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Postoperative emesis is common and a complicated subject to investigate because of its multifactorial nature. In spite of clinical impressions of a decrease in the incidence and severity for emesis, the documented incidence appears to have varied little over the past 40 years [1]; this may be a result, in part, to variability in the method of investigation. We propose a preliminary basis for risk stratification in order to standardize methodology for future studies.

One hundred and forty-seven patients undergoing minor orthopaedic surgery were studied prospectively by logistic regression analysis to determine the association of independent fixed patient risk factors with the incidence of postoperative emesis. Variable risk factors were controlled for all patients. The fixed factors of gender, history of previous emesis, postoperative opioids and an interaction between gender and previous emetic history were isolated as significant independent variables. History of motion sickness had a weak association with emesis. The probability of postoperative emesis in the first 24 h after surgery may be estimated from the equation: logit postoperative emesis = $-5.03+2.24(\text{opioids})+3.97(\text{previous emetic history})+2.4(\text{gender})+0.78(\text{motion sickness})-3.2(\text{gender}\times\text{previous emetic history})$ (log likelihood ratio test for 5 degrees of freedom, chi-square = 53.5; $P < 0.001$).

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EFFECT OF HALOTHANE ON [^{3}H]METHYLCHOLINE UPTAKE INTO RAT BRAIN SYNAPTOSOMES

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The plasma membrane has been implicated as a possible site of action of general anaesthetic agents. In order to test this hypothesis, we have investigated the effect of halothane on the uptake of choline, a precursor of acetylcholine, in a synaptosome preparation. Acetylcholine is an important neurotransmitter for the maintenance of consciousness.

Rat brain synaptosomes were prepared using a modification of the technique of Gray and Whittaker [1]. Halothane (2.4 rat MAC) was delivered to the synaptosome preparation and choline uptake was determined using an incubation media containing choline chloride 10 μmol $litre^{-1}$ labelled with [^{3}H]methylcholine. Maximum rate of reaction (Vmax) and Michaelis constant (K_m) were compared with data obtained from air controls using Student's paired *t* test.

Mean (SEM) Vmax and K_m values are shown in table IX. Halothane reduced Vmax significantly ($P = 0.002$). There was no significant change in K_m.

TABLE IX. *Mean (SEM)* V*max and* K_m *values in rat brain synaptosomes after halothane delivery and in air controls*

	Vmax (pmol mg^{-1} min^{-1})	K_m (μmol)
Air	1.19 (0.12)	3.61 (0.42)
Halothane	0.71 (0.08)	3.25 (0.50)

These data suggest that the uptake of choline is inhibited non-competitively by halothane. This is consistent with a generalized effect on the plasma membrane and differs from previous work which demonstrated that halothane inhibited the uptake of choline competitively [2].

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EFFECTS OF HALOTHANE ON CULTURED NEURONES

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Anaesthetics are known to diminish the calcium dependent components of action potentials in normal and cultured identified neurones of the mollusc *Lymnaea stagnalis* (L.) [1]. We report the effects of halothane, delivered at clinical concentrations, on a high-voltage-activated calcium current in voltage-clamped neurones in culture and also its effects on intracellular calcium concentration ($[Ca^{2+}]_i$) in both molluscan and rat hippocampal neurones in culture.

Identified neurones from the brains of *Lymnaea* and the related mollusc *Helisoma trivolvis* were isolated and cultured for 1–4 days, using standard techniques. Primary cultures of hippocampal neurones were obtained from halothane-anaesthetized 8–11-day-old Sprague–Dawley rat pups and were dispersed mechanically and cultured for 7–10 days. Calcium currents were recorded from molluscan neurones using the whole cell recording technique.

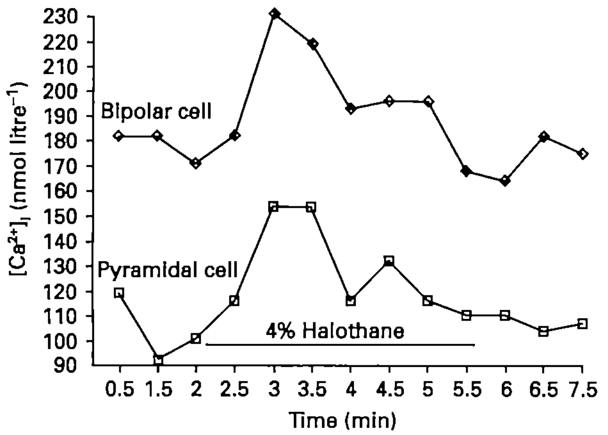

FIG. 1. Effect of halothane on intracellular calcium concentration ($[Ca^{2+}]_i$): 4% halothane increased $[Ca^{2+}]_i$ in dissociated hippocampal cells in zero calcium and EGTA saline.

Anaesthetics were prepared and delivered as described previously [2]. For experiments on $[Ca^{2+}]_i$, cells were loaded with the dual excitation dye FURA-2AM (2 μm, Molecular Probes) either by ester-loading or by direct injection in the case of molluscan neurones. Measurements of $[Ca^{2+}]_i$ were performed using fluorescence ratio microscopy.

A high-voltage-activated calcium current was recorded from cultured pedal I cluster neurones of *Lymnaea*. On exposure of these cells to increasing doses of halothane, the peak calcium current was reversibly depressed in a dose-dependent manner (e.g. by approximately 25% in 1% (vol/vol) halothane and by 90% in 4% halothane). These effects were rapid and occurred within 30 s of halothane perfusion.

Using similar bathing media, 2–4% halothane was found to cause a transient increase in $[Ca^{2+}]_i$ in cultured *Helisoma* neurones and in dissociated rat hippocampal neurones which lasted for several minutes and occurred even in the presence of zero calcium and EGTA saline (fig. 1). This indicates that the increase in $[Ca^{2+}]_i$ is a result of release from intracellular stores.

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FENTANYL INHIBITS EVOKED [^{3}H]NORADRENALINE RELEASE FROM HUMAN NEUROBLASTOMA CELLS

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The cellular mechanisms by which opioid drugs exert their clinical effects are still poorly understood, but may involve a process of neuromodulation. We used a human neuroblastoma cell line (SH-SY5Y) to examine opioid modulation of noradrenaline evoked release.

SH-SY5Y cells resemble sympathetic ganglion cells and, when differentiated, develop several characteristics of mature neurones, including an increase in intracellular noradrenaline content. These cells also possess μ-opioid, δ-opioid, M_3-muscarinic and α_2-adrenergic receptors and release of noradrenaline occurs in response to depolarization and muscarinic receptor stimulation.

[^{3}H]Noradrenaline release was measured in 6–8-day, retinoic acid 10 μmol litre^{-1}, differentiated, monolayer, cultured cells using a modification of the method of Murphy and colleagues [1]. Cells were incubated with [^{3}H]noradrenaline 40 nmol litre^{-1} in Krebs and HEPES buffer (pH 7.4) at 37 °C for 1 h. After three 15-min washes, the monolayers were challenged with potassium 100 mmol litre^{-1} or carbachol 1 mmol litre^{-1} in the absence or presence of fentanyl 10 μmol litre^{-1} for 3 min at 37 °C. Fentanyl was preincubated for 45 min. Unreleased [^{3}H]noradrenaline in the monolayer was extracted with perchloric acid 0.4 mol litre^{-1}. Data were analysed using Student's *t* test.

TABLE X. *Mean* (SEM) *[^{3}H]noradrenaline ([^{3}H]NA) release as percentage of the total amount of [^{3}H]NA in the monolayer before stimulation* (n = 5)

Stimulus	[^{3}H]NA release (%)
None	1.94 (0.08)
Potassium	6.50 (0.43)
Potassium + fentanyl	4.53 (0.05)
Carbachol	4.94 (0.22)
Carbachol + fentanyl	3.10 (0.17)

[^{3}H]Noradrenaline release is shown in table X.

The potassium- and carbachol-evoked release was reduced significantly (43% and 61%, respectively) ($P < 0.001$) when SH-SY5Y cells were exposed to fentanyl 10 μmol litre^{-1}. The mechanisms underlying this inhibition are currently under investigation.

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INHIBITION OF SODIUM–CALCIUM EXCHANGE INCREASES SKELETAL MUSCLE CONTRACTURE RESPONSE TO HALOTHANE

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It has been shown previously that amiloride affects the *in vitro* response of skeletal muscle from individuals susceptible to malignant hyperthermia (MH) after halothane exposure [1]. In cardiac sarcolemmal preparations, amiloride is known to block L- and T-type calcium channels, as well as the Na^+–Ca^{2+} exchanger [2]: any similar effect on skeletal muscle could account for the observations in our previous study [1]. In this study, we investigated the effects of benzamil, a derivative of amiloride which is a more specific Na^+–Ca^{2+} exchange inhibitor, on the *in vitro* responses of MH and normal skeletal muscle to halothane.

Patients attending for diagnostic muscle biopsy were typed according to the European MH Group procedure [3]. Using muscle specimens surplus to diagnostic requirements, the contracture responses to incremental additions of 0.5%, 1% and 2% halothane were recorded in the presence of benzamil 100 μmol litre^{-1}. These were compared to those obtained during the diagnostic halothane contracture tests.

Figure 2 shows the contracture responses to incremental additions of 0.5%, 1% and 2% halothane in MH susceptible muscle in the absence (MHS control) and presence (MHS benzamil) of benzamil 100 μmol litre^{-1} and also in normal muscle in benzamil 100 μmol litre^{-1} (MHN benzamil).

The force of contracture was significantly greater in the MHS benzamil group than in the MHS control group in response to 1% halothane (two-tailed paired *t* test: mean difference 3.78 g; 95% confidence interval (CI) 1.38 to 6.17 g; $P = 0.045$ with Bonferroni correction) and 2% halothane (two-tailed paired *t* test: mean difference 3.68 g; 95% CI 1.96 to 5.39 g; $P = 0.019$ with Bonferroni correction).

Na^+–Ca^{2+} exchange inhibition increased *in vitro* contracture responses of MH and normal muscle to halothane. The depressant effect of amiloride on MH muscle demonstrated previously may be a result of block of L- or T-type calcium channels.

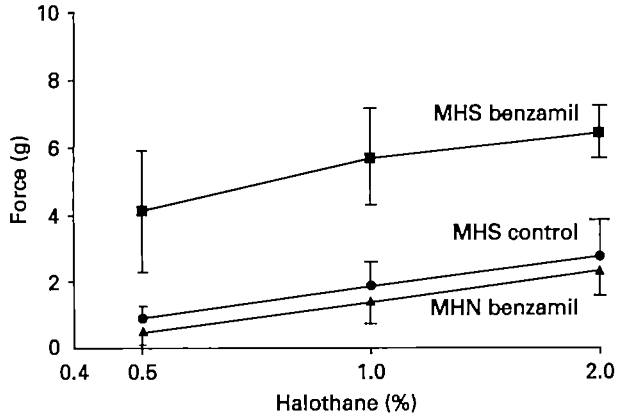

FIG. 2. Contracture response to halothane in MH susceptible muscle in the absence (MHS control) (●) and presence (MHS benzamil) (■) of benzamil and in normal muscle in benzamil (MHN benzamil) (▲) (mean and SD).

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ISOFLURANE INHIBITS INSULIN SECRETION FROM ISOLATED RAT PANCREATIC ISLETS OF LANGERHANS

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Halothane and enflurane inhibit insulin secretion *in vitro* [1]. We have studied the effects of isoflurane on insulin secretion from rat pancreatic islets of Langerhans *in vitro*, in static incubations and in a perifusion system.

Islets were isolated from fed Wistar rats by collagenase digestion [2] and incubated in a bicarbonate buffered salt solution (pH 7.4) for 30 to 60 min at 37 °C. For static incubations, groups of three islets were transferred to microcentrifuge tubes containing 100 µl of buffer as above. A reservoir of incubation medium was bubbled for 5 min with 100 % oxygen or with oxygen and isoflurane. Medium (500 µl) was then pipetted rapidly into each tube which was sealed and the preparation incubated for 30 min at 37 °C. A sample was then withdrawn and insulin measured by radioimmunoassay. The partial pressure of isoflurane in the gas phase above the incubation medium in the microcentrifuge tubes was measured by gas chromatography with flame ionization detection at 37 °C.

For the static incubations ($n = 7$–9), estimation of the partial pressure of isoflurane showed that the 1 % vaporizer setting was equivalent to 0.3–0.4 % and the 2 % isoflurane setting equivalent to 0.8–1.0 % after 30 min.

For perifusion, groups of 50 islets were perifused simultaneously with buffer in a 37 °C environment at a flow rate of 1 ml min^{-1}. The perifusate was collected at 2-min intervals for measurement of insulin content. After initial perifusion with glucose 5 mmol litre^{-1}, glucose 20 mmol litre^{-1} increased insulin secretion from the islets to 130–150 % of basal values within 2 min (table XI). After 20 min, the islets were perifused with buffer containing glucose 20 mmol litre^{-1} bubbled with 2 % isoflurane in oxygen, which inhibited insulin secretion within 2 min (table XI). Islets perifused subsequently with glucose 20 mmol litre^{-1} alone, showed a slow increase in insulin secretion, demonstrating that the inhibitory effect of isoflurane on secretion was reversible.

In conclusion, isoflurane reversibly inhibits glucose-stimulated insulin secretion in isolated rat islets of Langerhans.

TABLE XI. *Mean (SEM) insulin secretion (ng/islet 30 min^{-1}) from rat pancreatic islets of Langerhans, in a perifusion system, with glucose and glucose plus isoflurane*

	Insulin secretion
Glucose 5 mmol litre^{-1}	1.35 (0.60)
Glucose 20 mmol litre^{-1}	3.52 (0.62)
Glucose 20 mmol litre^{-1} + 0.5 % isoflurane	2.17 (0.20)
Glucose 20 mmol litre^{-1} + 1.0 % isoflurane	1.70 (0.20)
Glucose 20 mmol litre^{-1} + 2.0 % isoflurane	0.97 (0.43)

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EFFECT OF PROPOFOL AND THIOPENTONE ON FREE RADICAL-INDUCED HAEMOLYSIS

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Lipid peroxidation is a free radical-mediated process which can lead to mechanical disruption of cell membranes and which has been implicated in the lysis observed when red blood cells are exposed to an oxidant stress [1]. Since both propofol [2] and thiopentone [3] have been shown to inhibit lipid peroxidation *in vitro*, we examined the capacity of these agents to restrict free radical-induced haemolysis.

A 10 % erythrocyte suspension in isotonic buffered saline was prepared from heparinized blood donated by six healthy adults and exposed to an oxidant stress by adding ABAP (2,2′-azobis(amidinopropane)dihydrochloride, a water soluble azo compound which initiates lipid peroxidation) 100 mmol litre^{-1}. Haemolysis was measured every 30 min by spectrophotometric estimation of extracellular haemoglobin and the rate of haemolysis expressed as the time taken to reach 50 % haemolysis (H_{50}, min). The rates of haemolysis in control flasks (containing blood, ABAP and, for the propofol experiments, Intralipid) were compared with those from flasks containing propofol 12.5, 25 or 50 µmol litre^{-1} or thiopentone 62.5, 125 or 250 µmol litre^{-1} and analysed using ANOVA. Differences between flasks ($n = 6$ in each case) were analysed using a paired, two-tailed t test and quantified by confidence interval analysis.

Both propofol and thiopentone delayed significantly ABAP-induced haemolysis ($P < 0.0001$ in each case; ANOVA) (table XII). For propofol, the rates of haemolysis in the 25- and 50-µmol litre^{-1} flasks were significantly different from the controls ($P < 0.05$, $P < 0.001$, respectively; t test) as were the flasks containing thiopentone 125 and 250 µmol litre^{-1} ($P < 0.001$ in both cases; t test).

We conclude that both propofol and thiopentone contribute to the ability of the erythrocyte to resist oxidant-induced injury.

TABLE XII. *Rate of haemolysis, expressed as the time taken to reach 50 % haemolysis (H_{50}), in control flashes compared with those containing propofol or thiopentone*

	H_{50} (min)
Control	107 (90–125)
Propofol (µmol litre^{-1})	
12.5	126 (108–144)
25	150 (129–170)
50	182 (160–180)
Control	109 (104–113)
Thiopentone (µmol litre^{-1})	
62.5	117 (112–121)
125	126 (119–133)
250	138 (132–144)

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CONTINUOUS SUBARACHNOID INFUSION OF LOCAL ANAESTHETIC

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Extradural infusions of local anaesthetic or local anaesthetic and opioid mixtures are used to provide continuous analgesia during labour and in the postoperative period. These are usually low concentration, high volume solutions, for example 0.125% bupivacaine at 15 ml h^{-1}. One potential complication is migration of the extradural catheter into the subarachnoid space [1]. It has been claimed that a subarachnoid infusion resulting from such migration would cause a slow increase in the height of sensory block [2] and would be detected by hourly sensory testing and blood pressure measurement [3]. We could find no published data to support these claims. Recently, very fine catheters for use in the subarachnoid space have become available. Using such a catheter, we studied the effects of a deliberate infusion of low concentration, high volume local anaesthetic into the subarachnoid space.

After approval by the local Ethics Committee, six patients undergoing femoro–popliteal or femoro–femoral arterial bypass grafting gave informed consent and were enrolled in the study in an open fashion. Before surgery, after establishing venous access and applying ECG and non-invasive arterial pressure monitors, the patient was placed in the lateral position. Dural puncture was performed with a 22-gauge needle at the second lumber interspace and a 28-gauge catheter was passed 3 cm into the subarachnoid space. After securing the catheter to the skin and placing the patient in the supine position, correct placement of the catheter was confirmed by aspiration of CSF. Baseline recordings of arterial pressure and heart rate were obtained and an infusion of 0.125% bupivacaine was commenced at 15 ml h^{-1} using a syringe pump calibrated previously. Loss of pinprick sensation (27-gauge short bevel needle) and degree of motor block (Bromage scale) were assessed every 5 min. Heart rate and arterial pressure were recorded at the same intervals. The patients were attended continuously by the investigating anaesthetist.

One patient was withdrawn from the study because the pump was unable to infuse at the required rate through the 28-gauge catheter. The pattern of sensory block was similar in all patients (fig. 3). The onset of motor block followed a similar course. Heart rate and arterial pressure remained stable; no patient required i.v. fluids or vasopressors during the study period.

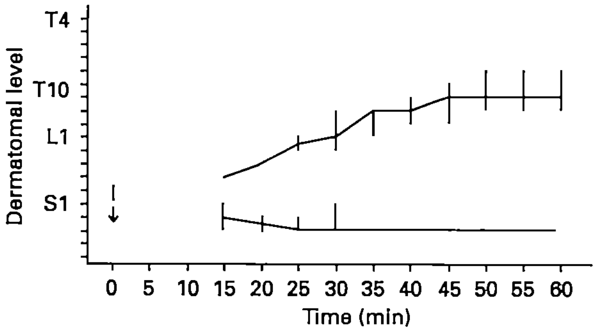

FIG. 3. Pattern of sensory block during subarachnoid infusion of 0.125% bupivacaine at 15 ml h^{-1}. Dermatomes below S3 were not tested (median and range). I = Start of infusion.

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PATIENT-CONTROLLED ANALGESIA AFTER THORACOTOMY: THORACIC EXTRADURAL *VS* I.V. FENTANYL

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Patient-controlled analgesia (PCA) is used widely, primarily to administer i.v. opioids in the postoperative period. Fentanyl, a potent short-acting opioid, has been shown to be useful when administered i.v. and is unlikely to accumulate in plasma [1, 2] when using PCA. Fentanyl may also be given by the extradural route and this has been shown to provide superior analgesia to i.v. fentanyl in labour at the same doses [3].

We studied 20 patients, after thoracotomy, in a double-blind randomized trial. Informed consent and Ethics Committee approval were obtained. After premedication with temazepam, general anaesthesia was induced with fentanyl, etomidate and a non-depolarizing neuromuscular blocker. Intubation of the trachea was performed and the lungs were ventilated with nitrous oxide in oxygen and enflurane. Group 1 ($n = 10$), randomized to receive i.v. fentanyl, had an i.v. cannula inserted for PCA purposes; group 2 ($n = 10$) received a thoracic extradural catheter for postoperative analgesia. Blinding was achieved by the theatre anaesthetist with the judicious use of non-transparent dressings and i.v. extension tubing to give the observer anaesthetist the impression that both the i.v. and extradural routes were to be used for postoperative analgesia. I.v. fentanyl was administered during operation and on recovery from anaesthesia to ensure that all patients were settled before assessment. The PCA system was programmed to administer fentanyl in 20-µg bolus doses in a concentration of 20 µg ml^{-1} with a lockout period of 5 min and no background infusion. Rescue analgesia was provided, if required, by titrated amounts of i.v. diamorphine. Pain, using a linear analogue pain score, sedation, fentanyl requirements, serum concentrations of fentanyl, arterial blood-gases, ventilatory frequency, arterial pressure, heart rate and adverse effects were assessed at 0, 20, 40 and 60 min, and at 2, 4, 6, 8, 16 and 24 h after recovery from anaesthesia. Results were compared using the Mann–Whitney *U* test, Student's *t* test for unpaired data and analysis of variance as appropriate (significance at $P < 0.05$).

One patient in group 2 was excluded because of insufficient data. There were no statistically significant differences between the groups in any of the variables measured. Two patients in group 1 and three patients in group 2 required rescue analgesia with diamorphine. Serum concentrations of fentanyl were similar in both groups as were fentanyl requirements.

It may be possible to achieve satisfactory analgesia in many patients after thoracotomy using PCA fentanyl either i.v. or extradurally. In this study, we were unable to demonstrate differences between the techniques.

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THE SITERITE ULTRASOUND MACHINE: AN AID TO INTERNAL JUGULAR VEIN CANNULATION?

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Central venous catheterization is an invasive procedure with a defined morbidity and a small, but acknowledged, mortality.

Various sites and techniques are used but the internal jugular vein approach is popular [1]. Ultrasound may be used to view neck vascular anatomy to assess the relative size and positions of both the carotid artery and the internal jugular vein [2], although the machines have a tendency to be large, complicated, expensive and are not readily available. The Siterite (Dymax) is a portable, lightweight, real-time ultrasound imaging system especially designed for viewing the internal jugular vein and carotid artery to assist cannulation of the internal jugular vein. This study was designed to assess its efficacy in aiding cannulation of the internal jugular vein.

After induction of anaesthesia, a right internal jugular vein catheter was inserted in 115 patients undergoing coronary artery bypass surgery using the Seldinger technique. A standard high approach was used, with insertion lateral to the pulsations of the carotid artery: the patients were in the Trendelenburg position. All cannulators were of at least registrar grade. In one group ($n = 58$) the Siterite was used before skin asepsis to explore vascular anatomy and in the other patients ($n = 57$), normal anatomical landmarks were used. Anticipated ease of insertion (using a four-point scale) was predicted in all patients using anatomical landmarks alone. Further prediction was made in the Siterite group after its use. After location of the internal jugular vein using a 21-gauge seeking needle, a guidewire was inserted into it through an 18-gauge cannula. The number of attempts of insertion of the seeking needle before the internal jugular vein was located was recorded, as was the time required to insert the guidewire from skin palpation. Actual ease of insertion and helpfulness of the Siterite was recorded on a four-point scale.

Patient characteristics were similar for the two groups. Use of the Siterite was found to be easy in all cases with visualization of the neck anatomy simple to obtain and interpret. After using the Siterite, the anticipated ease of cannulation was improved in comparison to that anticipated ($P = 0.04$) in the same subjects and also compared with the control group ($P = 0.01$; Mann–Whitney). Cannulation time for all cases, whilst not statistically different (Mann–Whitney), tended to be faster in the Siterite group compared with the controls (table XIII). It was reported to be useful in 47 cases.

TABLE XIII. *Cannulation results in the two groups of patients.* *P < 0.05 (*chi-square test*); †P < 0.05 (*Mann–Whitney test*)

	Siterite group ($n = 58$)	Control group ($n = 57$)
Failed cannulations (No. (%))	1 (1.7)	5 (8.8)
Successful cannulations within 100 s (No. (%))	43 (74.2)	31 (53.5)*
Successful first attempts (No. (%))	44 (75.6)	30 (52.6)*
Attempts per cannulation (mean (SD))	1.4 (0.9)	2.1 (1.6)†
Time per cannulation (s) (mean (SD))	104 (89)	141 (103)
Carotid artery puncture (No. (%))	3 (5.9)	3 (5.2)

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EFFECT OF ROCURONIUM AND VECURONIUM ON INTRAOCULAR PRESSURE

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Rocuronium may replace suxamethonium for rapid sequence induction [1]. For perforating eye injuries, this could be important. The present study investigated the effects of rocuronium and vecuronium on intraocular pressure (IOP), heart rate (HR) and arterial pressure (AP).

After Ethics Committee approval and written informed consent, 30 healthy patients undergoing elective ophthalmic surgery were allocated randomly to receive rocuronium 0.9 mg kg^{-1} or vecuronium 0.15 mg kg^{-1} i.v. After premedication with oxazepam 20–30 mg orally, anaesthesia was induced with fentanyl 2 μg kg^{-1} and propofol 2.5 mg kg^{-1}, and maintained with a propofol infusion of 6–12 mg kg^{-1} h^{-1}. Patients' lungs were ventilated with 100% oxygen by mask (end-tidal carbon dioxide concentration 4.5–5 kPa). After induction, baseline recordings of HR, AP (Dinamap) and IOP (Tonopen) were obtained. When stable anaesthesia had been achieved, rocuronium or vecuronium was injected and HR, AP and IOP were measured at 30, 90, 150, 210, 270 s. At 300 s, the patients' tracheas were intubated and recordings repeated at 30, 120 and 240 s after intubation. At 240 s, patients received 60% nitrous oxide in oxygen and measurements were obtained after 60 s. Differences between groups were analysed using the Wilcoxon rank sum test. $P < 0.05$ was regarded as significant.

Patient characteristics were similar in the two groups. Rocuronium caused a significant increase in HR at 210 s (mean percentage change from baseline 5.1 (SEM 2.1)%) and 270 s (7.5 (2.3)%) and an increase in mean AP at 30 s (9.1 (2.3)%), 90 s (5.2 (1.3)%), 150 s (7.5 (2.1)%) and 210 s (6.2 (2.0)%). Vecuronium had no cardiovascular effects. Rocuronium and vecuronium had similar effects on IOP; a significant decrease occurred at 210 s (9.7 (4.6)% *vs* 12.4 (4.3)%, respectively). Intubation produced much greater changes in HR, AP and IOP than those seen after either rocuronium or vecuronium. The changes produced by intubation in the two groups were not significantly different. In both groups, IOP had returned to preintubation values 4 min after intubation. Nitrous oxide had no effect on IOP after 60 s.

Both drugs produced a significant effect on IOP. Rocuronium produced small, but significant increases in HR and AP. Increases in HR after rocuronium have been reported previously [2].

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PHARMACODYNAMICS OF MIVACURIUM CHLORIDE IN THE CIRRHOTIC PATIENT

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The non-depolarizing neuromuscular blocking agent, mivacurium chloride, is metabolized by plasma cholinesterase [1], the activity of which may be reduced in patients with liver disease [2]. We compared the pharmacodynamics of this drug in cirrhotic patients and in a healthy control group.

Twenty cirrhotic patients (Child's group A, B, or C [3]) and 10 healthy patients with normal hepatic function were included in the study. In each patient, plasma cholinesterase activity, dibucaine and fluoride number were measured before surgery. Anaesthesia was induced with fentanyl 1 μg kg^{-1} and thiopentone 3–5 mg kg^{-1}, followed by a period of spontaneous ventilation of at least 15 min, during which time 70% nitrous oxide in oxygen with isoflurane was administered to achieve a stable end-tidal isoflurane concentration of 0.5%. Supplementary doses of fentanyl were given as appropriate. After induction of anaesthesia, EMG monitoring was started using a Medelec MS6. Train-of-four stimuli were applied every 12.5 s to the ulnar nerve and the surface compound action potential of the adductor pollicis muscle measured. When the end-tidal isoflurane concentration stabilized, a bolus of mivacurium chloride 0.15 mg kg^{-1} was given. The EMG response was recorded throughout the study until T1/T0 had recovered to at least 85% and T4/T1 to at least 80%. No anticholinesterase was given. The resulting EMG trace was analysed and the maximum depression of T1/T0 (%), together with the times to 95% depression, 10% and 25% recovery of T1/T0, the recovery index (25–75% T1/T0) and 70% recovery of T4/T1 were noted. Differences in these variables between the healthy and cirrhotic patients were analysed using the Mann–Whitney *U* test. The correlation of the measures of recovery with cholinesterase activity was assessed using Pearson's correlation coefficient.

TABLE XIV. *Mean* (SD) *pharmacodynamic variables for onset and recovery in the two groups.* *$P < 0.05$; ***$P < 0.001$ *between groups*

	Control group ($n = 10$)	Cirrhotic group ($n = 20$)
95% Depression T1/T0 (min)	2.79 (0.94)	2.20 (0.56)*
Max. depression (%)	98.66 (1.31)	98.22 (4.25)
10% Recovery T1/T0 (min)	13.43 (2.94)	22.51 (9.47)***
Recovery index (25–75% T1/T0)	8.34 (4.12)	14.74 (14.05)*
T4/T1 = 0.7 (min)	27.39 (4.83)	45.61 (21.98)***

Mean (range) cholinesterase activity in healthy patients was 1124 (574–1511) iu litre^{-1} and in cirrhotic patients 605 (200–1432) iu litre^{-1} ($P < 0.001$). All patients had normal dibucaine and fluoride numbers. There was a strong negative correlation between plasma cholinesterase activity and 25% recovery for all patients ($r = -0.72$; $P < 0.0001$).

The cirrhotic group contained 10 Child's A, eight Child's B and two Child's C patients. There were no significant differences between Child's A and Child's B patients in any of the measured EMG variables.

Although onset of neuromuscular block was more rapid in the cirrhotic group (table XIV), duration of block was increased greatly. Time to 25% recovery of T1/T0 was found to be related to cholinesterase activity.

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INFLUENCE OF CIRCULATING DRUG ON RECOVERY OF NEUROMUSCULAR BLOCK IN THE ISOLATED FOREARM

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Feldman and Tyrrell [1] ascribed the slow decay of neuromuscular block in the isolated arm to be a function of drug–receptor association. However, Hull [2] and Stanski and Sheiner [3] reasoned that the plasma concentration after tourniquet release would be sufficient to prolong recovery and to produce the increase in block which occurs for a short time afterwards. To test this hypothesis, we administered a repeat dose of non-depolarizing agent during offset of block, at the same degree of block as that achieved when the tourniquet was deflated during onset.

Three groups of five experiments were performed on three healthy volunteers. A vein on the dorsum of the hand was cannulated, a 2-kg load cell with a thumbpiece modification was secured and a standard pre-tension applied. The ulnar nerve at the wrist was stimulated using a supramaximal 0.2-ms square wave impulse at a frequency of 0.2 Hz. The resultant adductor pollicis twitch was amplified and recorded on a Gould paper chart recorder. After a 5-min period of stabilization, a forearm tourniquet was inflated to a pressure of 300 mm Hg and vecuronium 0.3 mg in 20 ml of saline was injected i.v. to produce paralysis via retrograde spread. In groups I and II, the tourniquet was released at 3 min: group I was used as a control. In group II, at 10% recovery of twitch height, a repeat dose of vecuronium 0.3 mg was administered into the systemic circulation. In group III, the tourniquet was released at 50% twitch depression and the repeat dose of vecuronium given when the twitch height had recovered to that level. The 25% to 75% T1 recovery indices were measured from the hardcopy of each experiment. The means of the groups were compared using unpaired *t* tests.

Mean tourniquet times were 3 min in groups I and II and 1 min in group III. All traces developed increased block after tourniquet release, unless complete block had already become established at that time. However, there was no noticeable effect on the recovery slope when the second dose of neuromuscular block was given in groups II and III. The mean (SD) 25–75% recovery indices in groups I, II and III were 9.2 (2.4), 8.7 (1.2) and 9.9 (1.9) min, respectively.

It would appear that the plasma concentrations resulting from the systemic administration of vecuronium 0.3 mg are insufficient to effect increased block in the isolated forearm or to affect its subsequent recovery.

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RECORDING ELECTRODE IMPEDANCE HAS NO EFFECT ON EVOKED EMG RESPONSES

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Changes in skin–electrode impedance have been thought to be responsible for the failure of EMG responses to return to baseline during the offset of neuromuscular block [1]. The skin–electrode impedance is related inversely to temperature at low current density [2], but a relationship between skin–electrode impedance and EMG response has not been demonstrated. Skin puncture reduces the skin–electrode impedance and decreases movement artefact in ECG recordings [3]. This may also be useful during EMG monitoring.

Thirty ASA I patients undergoing minor surgery were allocated randomly to receive either no skin puncture ($n = 15$) or six 1-mm deep skin punctures over the belly of the first dorsal interosseous muscle using a Heaf gun ($n = 15$). Before induction of anaesthesia, the skin at the EMG monitoring site was rubbed for 5 s with a gauze swab soaked in 70% isopropyl alcohol. The skin was punctured where indicated and electrodes (Nikomed 4610) were attached to the patient; the ulnar nerve was stimulated at the wrist and the EMG response recorded over the first dorsal interosseous muscle using a Relaxograph. The hand was held in a fist, thumb on the outside, with a piece of 10-cm adhesive tape. The resistance and capacitance between the recording electrodes were measured at 100 Hz and 1000 Hz using a calibrated impedance bridge (AVO B184) and the electrode offset potential was measured with a digital multimeter (Fluke 75). A standard anaesthetic technique was used with non-depolarizing neuromuscular block and IPPV: the Relaxograph was calibrated when the patient was asleep. At the end of surgery, residual neuromuscular block was antagonized with neostigmine. EMG monitoring was continued until the train-of-four ratio was 1.0 and the EMG response was stable, and the resistance, capacitance and offset potential were measured again.

In the puncture group, the median final EMG response was 83% (interquartile range 73–96%) and in the non-puncture group 81% (65–91%) ($P = 0.43$; Fisher's exact test). The skin–electrode impedance decreased in all patients except one in each group. There was no difference between the groups in skin–electrode impedance or offset potential nor was there any relationship between the change in skin–electrode impedance or offset potential and the final EMG response.

The decrease in EMG response observed frequently during offset of neuromuscular block is not the result of an increase in skin–electrode impedance. Skin puncture is not useful for preventing the reduction in EMG response.

ACKNOWLEDGEMENT

This study was supported by grants from the Northcott Devon Medical Foundation and the League of Friends of Plymouth General Hospital.

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HEART RATE SPECTRUM ANALYSIS DURING INDUCTION OF ANAESTHESIA WITH THIOPENTONE OR PROPOFOL

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Autonomic function may be affected significantly by anaesthesia. Spectral analysis of beat-to-beat variability in heart rate (HR) provides a non-invasive assessment of autonomic function [1]. Previous studies have investigated the effects of combinations of anaesthetic drugs on HR variability [2, 3]. The different drugs may produce either their own effects or interact with one another. Thus in the present study we compared the effects of thiopentone or propofol alone on HR variability in unpremedicated ASA I or II patients.

Eighteen patients (six female, aged 21 to 65 yr; weights 54 to 90 kg) undergoing elective surgical procedures were allocated randomly to receive a dose of either thiopentone or propofol sufficient to obtund the eyelash reflex, followed by two increments of approximately 25 % of the initial dose at 3 and 6 min. Patients breathed oxygen throughout the study; thereafter anaesthesia was continued according to clinical needs.

HR was measured from the ECG and ventilatory frequency obtained by impedance plethysmography. Spectral density of the resting HR within the frequency band 0.04–0.10 Hz (low frequency power (LFP)) and a 0.12-Hz band width at the ventilatory frequency mode (ventilatory frequency power (VFP)) were calculated in realtime every 200 s by fast Fourier transformation using a microcomputer. It has been demonstrated previously that LFP is determined by combined sympathetic and parasympathetic activity while VFP reflects parasympathetic activity alone [1]. Data were collected during the following periods: two periods before induction of anaesthesia, during induction of anaesthesia and after administration of the two incremental doses. HR variability was expressed for each period as total power (LFP+VFP) and as normalized low frequency power (LFPn: LFP/LFP+VFP). The latter reflects the relative contribution of sympathetic activity to HR variability.

There was a decrease in total power between the periods before and after induction of anaesthesia. The mean values for total power before induction (arbitrary units) were 5.275 (SD 3.448) for the thiopentone group and 6.358 (4.705) for the propofol group. There was a significant decrease in total power after administration of the first and second incremental doses compared with values before induction ($P < 0.05$; ANOVA and Scheffe's test). There was no significant change in LFPn during or after induction. No significant differences in these variables of HR variability were found between the thiopentone and propofol groups (table XV).

These data indicate a decrease in overall HR variability after induction of anaesthesia, but no change in the balance between sympathetic and parasympathetic activity for either anaesthetic induction agent.

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EFFECT OF BRIEF HYPOXAEMIA ON THE RESTING ECG IN PATIENTS WITH EXERCISE-INDUCED CARDIAC ISCHAEMIA

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Episodic oxyhaemoglobin desaturation occurring during sleep is common after operation [1] and may be associated with derangements in heart rate, rhythm, arterial pressure or of the ST segments on the ECG. Effects of periods of hypoxaemia on the brain have been documented but the cardiovascular implications are not clear. In postoperative patients, ECG changes indicative of ischaemia have not been linked conclusively with any associated periods of hypoxaemia, but may be associated with tachycardia or hypertension. The purpose of this study was to evaluate the effect of short periods of hypoxaemia on the ECG in patients with ischaemic heart disease, in the absence of other precipitating factors such as pain and the effects of sleep.

After approval of the hospital Ethics Committee, 38 subjects undergoing routine exercise ECG testing consented to take part in the study. After recovery from the exercise test, each subject breathed an oxygen–nitrogen mixture to reduce Sp_{O_2} to 85 % for 3 min. Throughout this period, the 12-lead ECG was monitored continuously and analysed by computer. The subject breathed 100 % oxygen for 1 min after the period of hypoxaemia.

The 38 subjects comprised volunteers (3), and those with chest pain (20), recent myocardial infarction (11), palpitations (2) and others (2). The exercise ECG test results were assessed by a consultant cardiologist and divided into three groups: positive, equivocal and negative, based on the criteria of Chung [2]. The results are shown in table XVI.

Symptoms during the hypoxaemia test, elicited by direct questioning, were mild dyspnoea (7), dizziness (8) and chest tightness (2). The two patients in the last group showed no ECG

TABLE XV. *Mean* (SD) *total power* (*LFP+ VFP*), *normalized low frequency power* (*LFPn*) (*arbitrary units*) *and heart rate* (*HR*) *in the propofol and thiopentone groups before induction of anaesthesia* (*1, 2*), *after induction* (*3*) *and after administration of the first* (*4*) *and second* (*5*) *incremental doses.*

	1	2	3	4	5
HR (beat min^{-1})					
Thiopentone	57.21	57.71	65.24	61.97	60.43
	(10.77)	(11.06)	(8.19)	(7.09)	(7.31)
Propofol	53.19	54.60	65.45	60.82	59.97
	(10.27)	(10.55)	(9.55)	(8.74)	(8.00)
LFP+VFP					
Thiopentone	4.342	5.255	3.189	1.881	2.176
	(2.940)	(3.473)	(1.714)	(1.370)	(2.155)
Propofol	6.155	7.758	4.410	3.780	2.600
	(3.819)	(5.664)	(3.371)	(4.727)	(3.762)
LFPn					
Thiopentone	0.805	0.809	0.827	0.723	0.721
	(0.124)	(0.088)	(0.066)	(0.202)	(0.229)
Propofol	0.668	0.744	0.812	0.763	0.860
	(0.165)	(0.134)	(0.094)	(0.198)	(0.065)

TABLE XVI. *Mean (95% confidence intervals) ST values (mm). Significant differences: **P < 0.01, exercise compared with hypoxaemia test; ††P < 0.01, positive compared with negative result*

Exercise result	n	ST decrease (Exercise)	ST decrease (Hypoxaemia)
Positive	11	2.48 (1.9–3.2)**††	0.18 (0.01–0.35)††
Equivocal	5	1.5 (0.7–2.3)	0.1 (−0.16–0.36)
Negative	22	1.1 (0.9–1.3)	−0.08 (−0.17–0)

evidence of ischaemia during hypoxaemia. Generally the symptoms were mild and spread across all groups. In contrast, symptoms during the exercise test were volunteered, often severe enough to stop the test and were more common in the exercise positive group.

We conclude that a 3-min period of hypoxaemia at Sp_{O_2} 85 % does not, in the absence of other precipitating factors, cause changes in the ST segment indicative of ischaemia.

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COMPARISON OF THE EFFECTS OF METHOXAMINE AND PHENYLEPHRINE ON MIDDLE CEREBRAL ARTERY VELOCITY DURING CAROTID ENDARTERECTOMY

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Phenylephrine has been used widely to maintain arterial pressure during carotid endarterectomy, although its use has been linked with myocardial ischaemia [1]. Methoxamine has not been used widely and little is known of its effect on cerebral blood flow during carotid endarterectomy. This study was designed to compare the effects of methoxamine and phenylephrine on time-averaged maximum velocity of blood flow in both middle cerebral arteries (*V*mca) during carotid endarterectomy.

After Ethics Committee approval and informed consent, 20 patients undergoing carotid endarterectomy were allocated randomly to receive methoxamine or phenylephrine for maintenance of systolic arterial pressure (SAP) during carotid endarterectomy. Anaesthesia was induced with fentanyl 4–6 μg kg^{-1}, etomidate 0.1 mg kg^{-1} and atracurium 0.5 mg kg^{-1} and maintained with 67 % nitrous oxide in oxygen and 0.5–1.5 % enflurane. End-tidal carbon dioxide was maintained in the range 4.9–5.2 kPa. Before shunt insertion and while the shunt was open during carotid endarterectomy, SAP was increased from 25–30 mm Hg less than the patient's awake SAP to 25–30 mm Hg greater than the awake SAP by infusion of either methoxamine 10–40 mg h^{-1} or phenylephrine 2–5 mg h^{-1}. Before and after SAP was altered, *V*mca was measured with two 2-MHz transcranial Doppler transducers which were positioned over the right and left temporal windows [2].

There were no significant differences between the two groups of patients in age, weight, systolic or diastolic arterial pressure before surgery. During enflurane anaesthesia, *V*mca decreased compared with awake *V*mca on both sides (40 to 28 cm s^{-1} on the ipsilateral side and 43 to 30 cm s^{-1} on the contralateral side) ($P < 0.01$; paired *t* test). Methoxamine increased *V*mca significantly on the ipsilateral side before shunt insertion (28 to 35 cm s^{-1}) and while the shunt was open (29 to 33 cm s^{-1}) ($P < 0.05$; paired *t* test), whereas phenylephrine had no effect. The mean value for the slopes of *V*mca/SAP in the methoxamine group on the ipsilateral side before shunt insertion (1.08 cm s^{-1} 10 mm Hg^{-1}) was significantly steeper than that of the phenylephrine group (0.14 cm s^{-1} 10 mm Hg^{-1}) ($P < 0.05$, Mann–Whitney test).

We believe methoxamine to be preferable to phenylephrine for maintaining cerebral perfusion during carotid endarterectomy.

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PRESSOR RESPONSE TO VENOUS CANNULATION AND EFFECT OF LOCAL ANAESTHETIC INFILTRATION

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There has been no previous study on the effect of venous cannulation on the cardiovascular system. Work in our department [1] has shown that the pain of cannulation is reduced significantly by the use of subcutaneous local anaesthetic infiltration before cannulation. We have monitored mean arterial pressure (MAP) and rate–pressure product (RPP) during and immediately after venous cannulation to investigate if any change in these variables could be attenuated by the use of local anaesthetic before cannulation.

After District Ethics Committee approval, 40 adult patients undergoing elective surgery were allocated randomly into two groups: group 1, cannulation alone (18-gauge Venflon); group 2, subcutaneous infiltration of 1 % lignocaine 0.25 ml via a 25-gauge needle before cannulation. A Finapres non-invasive arterial pressure monitor (Ohmeda 2300) was used to measure baseline values of heart rate, systolic and MAP after a stabilization period of 5 min. Further readings were obtained at the time of cannulation and at 30 s, 1, 2 and 3 min thereafter. In group 2, local anaesthetic infiltration was performed at time 0 and cannulation at 1 min. All cannulations were successful at the first attempt. Changes in RPP and MAP from baseline at each time interval were calculated. Results were analysed using two-way analysis of variance.

Forty patients completed the trial. The groups were comparable in age and sex and there was no significant difference in baseline values between the two groups. The mean changes in MAP from baseline values are shown in figure 4. After local infiltration, there was no significant difference in MAP or RR from baseline readings. Patients receiving cannulation alone showed a significant increase in both variables. The effect of lignocaine was confirmed using two-way analysis of variance ($P < 0.005$).

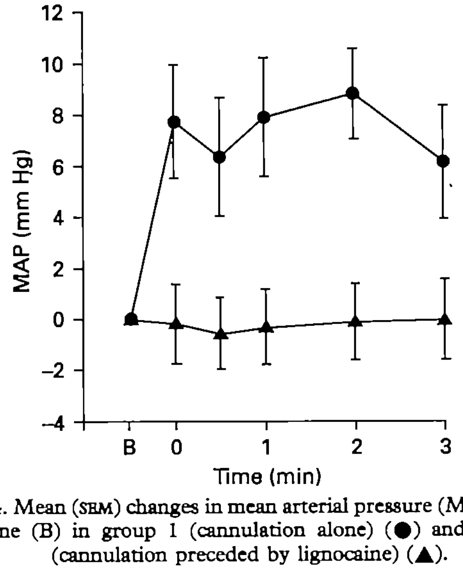

FIG. 4. Mean (SEM) changes in mean arterial pressure (MAP) from baseline (B) in group 1 (cannulation alone) (●) and group 2 (cannulation preceded by lignocaine) (▲).

We conclude that there is a significant pressor response to venous cannulation which is abolished by the use of local anaesthetic infiltration before cannulation.

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OXYGEN UPTAKE DURING REBREATHING IN A MAPLESON A SYSTEM

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Various investigators have reported an increase in the inspiratory–expiratory oxygen concentration difference when fresh gas flow into the Mapleson A system was reduced progressively [1, 2]. This suggests that pulmonary oxygen uptake increases. Therefore, we quantified oxygen uptake in volunteers during rebreathing.

Ten ASA I (eight males, weights 49–90 kg) trained volunteers were studied using a Mapleson A system. After a period of familiarization, baseline recordings were made at fresh gas flows in excess of predicted minute ventilation (*V*E). Fresh gas flow (*V*F) was reduced incrementally until the two points of rebreathing occurred: RP1 [1] and RP2 [3]. Continuous measurements of the concentration of oxygen and carbon dioxide in the respired gases were obtained using a mass spectrometer. Respiratory flow was measured using a pneumotachograph (Fleisch 2) and integral of flow was used to determine respiratory volumes. The signals from these instruments were digitized at 200 Hz onto a Macintosh microcomputer for calculation of oxygen uptake, using the difference in inspiratory–expiratory oxygen content.

TABLE XVII. *Mean* (SD) *changes in fresh gas flow* (VF), *minute ventilation* (VE) *and oxygen uptake at baseline and at the two points of rebreathing* (*RP1, RP2*). *Significant differences* (*ANOVA*): *P < *0.05 compared with baseline*; †P < *0.05 compared with RP1*

	Baseline	RP1	RP2
*V*F/*V*E	1.3 (0.1)	0.8 (0.1)	0.6 (0.1)
Oxygen uptake (STPD ml kg^{-1} min^{-1})	4.0 (0.7)	5.2 (1.2)*	7.5 (2.0)*†
*V*E (ml kg^{-1} min^{-1})	99 (21)	131 (34)*	201 (38)*†

There was an apparent increase in oxygen uptake when rebreathing occurred with a significant difference between the two sets of criteria for rebreathing (table XVII).

ACKNOWLEDGEMENT

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COHERENCE IN THE AUDITORY EVOKED RESPONSE AS A MEASURE OF AROUSAL DURING ANAESTHESIA

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The auditory steady state response to 40-Hz clicks relies on there being a 25-ms inter-peak latency of the early cortical waves Na and Nb seen in the transient auditory evoked response. Jones [1], using a 6-Hz stimulus rate, demonstrated a change in both amplitude and latency of these waves during anaesthesia and surgical stimulation. This change in latency suggests that there would be a change in the 40-Hz steady state response during anaesthesia. A change in steady state response amplitude has been shown during isoflurane anaesthesia [2]. However, because of the increase in latency shown previously [1], we predicted that the critical stimulating frequency necessary to generate the steady state response would decrease.

To confirm this prediction, we developed a method of sweeping the stimulus frequency from 47 Hz to 5 Hz (in 1-Hz steps) in six volunteers, and, on computing the Fourier transform of the averaged response at each frequency, a coherent effect was demonstrated in the steady state response. This coherence was characterized by a dominant fundamental frequency in the steady state response with minimal harmonic content. This dominant frequency correlated with changing end-tidal isoflurane concentration.

A tetanic (100-Hz) supramaximal electrical stimulus was applied as an arousal stimulus equivalent to surgical incision [3] and this produced an increase in coherent frequency analogous to a decrease in isoflurane concentration.

In conclusion, this is a new technique for assessing changes in the early cortical waves of the AER during various stages of anaesthesia. It has the advantage of dependence on arousal, rapid data acquisition, independence of amplitude and is possibly without hysteresis.

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POSTER PRESENTATIONS

EFFECT OF AGE ON THE SENSITIVITY OF UPPER AIRWAY REFLEXES

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General reflex activity decreases with age and ankle jerks are found in only 30% of subjects more than 65 years of age. Furthermore, the elderly may have an increased risk of aspiration after general anaesthesia and sedation [1]. Pontoppidan and Beecher found a sixfold decrease in the sensitivity of the upper airway reflexes from the second to the eighth and ninth decades [2].

A new method of measurement of the sensitivity of upper airway reflexes has been described using dilute ammonia as a chemical stimulus to the upper airway; the ammonia threshold (NH_3TR) is the lowest concentration required to elicit a "glottic stop". Using this method, a glottic stop is defined as a rapid decrease in inspiratory flow, the flow decreasing by at least 25% of peak, followed by a swift recovery. The whole event lasts less than 0.5 s [3]. The aim of this study was to measure NH_3TR over a wide age range to quantify the effect of increasing age on the sensitivity of upper airway reflexes.

Eighty-seven healthy, non-smoking volunteers (30 female) aged 17–96 yr were investigated. Exclusion criteria included asthma, chronic lung disease, mental or neurological impairment and sedative medication. NH_3TR was measured in each subject using a technique described previously [3] and the thresholds plotted against age.

We found that sensitivity of upper airway reflexes to an ammonia stimulus decreased with increasing age (fig. 5).

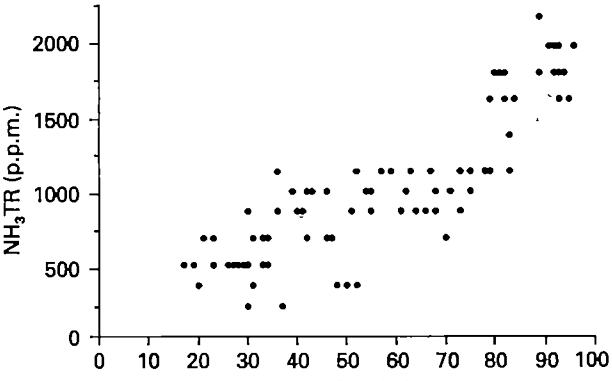

FIG. 5. Influence of age on the sensitivity of upper airway reflexes using the ammonia threshold (NH_3TR) method.

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WHERE IS THE BOBBIN?

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One of the common hazards of anaesthesia is inadvertent change of the oxygen or nitrous oxide fresh gas flows because of accidental rotation of the needle valves or failure of gas supply. We demonstrate a simple prototype gadget using readily available components (Radio Spares Components Ltd) which is capable of detecting displacement of the bobbin in the rotameter of the anaesthetic machine. The unit, which can be made the size of a wrist watch, may be clipped by the anaesthetist to the rotameter system in front of the bobbin after the desired gas flow has been set. If the bobbin is displaced out of alignment, for any reason, the device will bleep. Different warning tones could be built into the devices to correspond to different gases.

The battery-driven unit consists of four modules, a pulsed infra-red transmitter, an infra-red detector, a logic circuit and an alarm oscillator. The infra-red transmitter–detector uses components found in household remote controls and operates in a pulsed mode to prolong battery life. The detector is adjacent to the transmitter and monitors the amplitude of pulses reflected from the bobbin. Loss of reflected pulse amplitude occurs when the bobbin is out of alignment with the unit. The logic circuit detects the loss in pulse amplitude and triggers the alarm oscillator. The alarm is in a standard wrist watch Piezoelectric sound element. Mass production of this device should allow a unit price of less than £20 (details are available from the authors).

DESCRIBING CIRCLE SYSTEMS

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The performance of a circle system depends on the relative positions of the components. This has been shown by a number of workers [1]. Description of a circle system has hitherto required a diagram showing all the components assembled in their relative positions. This inhibits discussion and the easy exchange of ideas, which was recognized by earlier workers [2]. We present a notation which aims to simplify and compress the description of any circle system into a single line of alpha-numeric characters reproducible on the simplest of typewriters.

For the purposes of the notation, circle systems were divided into three segments by their relation to the site of entry of the fresh gas flow (FGF) and the two flow directing valves: segment one lies between the FGF and the inspiratory valve; segment two lies between the flow directing valves; and segment three lies between the expiratory valve and FGF.

Each component is represented by an abbreviation of not more than three letters associated with the number of the segment in which the component lies. Within each segment three positions are defined: if the component is at the beginning of the segment the abbreviation for it precedes the number of segment; if the component is at the end of a segment the abbreviation follows the segment number; and if the component lies in a central position the abbreviation is both preceded and succeeded by the segment number. An oblique stroke separates the description of each component.

The patient is a component of the system whose proximity to the circulating valves is indicated by the addition to the patient abbreviation (PT) of either N (near) or F (far). This is necessitated by clinical practice. Suitable abbreviations include: CAN = canister, BAG = reservoir bag, PT = patient, APL = adjustable pressure limiting valve, VAP = vaporizer, VEN = ventilator, CIR = circulator. Using this notation a commonly used system is written as 2PTF/3BAG3/3APL3/3CAN3.

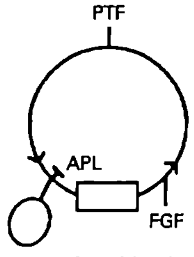

FIG. 6. A circuit diagram produced by the string 2PTF/3BAG3/3APL3/3CAN3. PTF = Patient far; APL = adjustable pressure limiting valve; FGF = fresh gas flow.

A computer program has been written which prints out a circuit diagram on typing in the appropriate string. Figure 6 was generated by the string above.

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USE OF NASAL OXYGEN CANNULAE TO MONITOR POSTOPERATIVE BREATHING

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The measurement of nasal gas flow with nasal cannulae has been described [1]. We report our experience using a modified system to monitor nasal flow in patients during the nights after upper abdominal surgery.

Oxygen from a wall outlet or cylinder passes through two rotameters: one supplies oxygen to the patient's nasal cannulae at a flow rate of 2 litre min^{-1}; the other supplies oxygen to a second "reference" pair of nasal cannulae and its flow rate is adjusted so that when there is no nasal gas flow, the pressure measured by an electronic differential pressure transducer connected between the patient cannulae and the reference cannulae is zero. As the patient breathes, the flow of gas in and out of the nose causes a decrease and increase in the pressure in the patient's nasal cannulae relative to that in the reference cannulae. The pressure difference is transduced, displayed on an oscilloscope and recorded on tape together with other respiratory signals.

Seventeen patients have been monitored during the first two nights after upper abdominal surgery (34 nights of monitoring, 6 h each night). A video camera was used to record the position of the nasal cannulae. The ward staff were not able to see the flow signal which was being recorded.

A good nasal flow signal was obtained throughout the monitoring period on 22 nights. Pressure changes measured during inspiration and expiration varied between patients and within patients over the course of the night and were usually between ± 1 mm H_2O and ± 5 mm H_2O. Episodes of apnoea could be identified and comparison with simultaneously recorded respiratory inductive plethysmography traces enabled the apnoeas to be classified as central or obstructive.

On 7 nights there were periods of poor or absent nasal flow signal caused by partial displacement of the nasal cannulae (15 episodes of median duration 20 min; interquartile range 4–75 min; range 1–330 min) and on one night the signal was lost because the system needed to be reset. If the ward staff had been able to see the flow signal, the nasal cannulae may have been put back into the correct position more promptly. However, on 4 nights there were periods of poor or absent nasal flow signal caused by the patient breathing entirely, or almost entirely, through the mouth (32 episodes of median duration 5 min; interquartile range 1.5–12 min; range 1–74 min).

When this system was used in an earlier study in which 15 patients were observed continuously during the night after upper abdominal surgery [2], oxygen delivered through the nasal cannulae completely prevented episodes of hypoxaemia ($Sp_{O_2} < 90\%$) in all patients.

ACKNOWLEDGEMENT

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PREOPERATIVE SILENT ISCHAEMIA IS RELATED TO HYPERTENSION

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We have reported previously a 16 % incidence of silent ischaemia in a general surgical population and that high-risk groups for silent ischaemia exist [1]. Pre-existing hypertension has been considered a potential predictor of preoperative silent ischaemia [2]; our data and that of Lutsch and colleagues [3], however, have failed to confirm hypertension as a useful marker. But it is possible that, within a hypertensive population, the quality of hypertensive control could influence the incidence of silent ischaemia, and therefore we decided to reassess our general surgical population.

One hundred and fifty-six patients aged more than 40 yr, undergoing elective surgical procedures, gave informed consent to the study. All were interviewed, a full examination conducted and results of preoperative investigations noted. A solid state, ambulatory ECG was fitted to record leads II and V5 for 8–24 h before operation (mean 16.7 h). Hypertension was defined as a diastolic pressure greater than 100 mm Hg for at least 48 h or a history of past or ongoing antihypertensive therapy. The terms incidental and poor control were used to indicate a diastolic arterial pressure greater than 100 mm Hg with either no previous diagnosis of hypertension or ineffective therapy in progress. Good control implied a diastolic pressure smaller than 100 mm Hg. Comparisons were made using the chi-square test with Yate's correction.

Of the 156 patients studied, 80 were normotensive and 76 hypertensive. With respect to incidence of silent ischaemia, the hypertensive patients were subdivided into good control, poor control and incidental hypertensives. The poorly controlled and incidental hypertensives together defined a group with an incidence of silent ischaemia of 52.9 % ($P < 0.001$) (table XVIII). Those with good control were made up of a number of different therapy subgroups, including those in whom therapy had been discontinued and arterial pressure was normal. In no case did an individual subgroup have an incidence of silent ischaemia significantly different from the normotensive group.

Our results provide evidence that untreated or poorly controlled hypertension is associated with an inordinately and potentially harmful increase in silent ischaemia. It is also clear that control of hypertension affords protection with respect to silent ischaemia, irrespective of the specific drug therapy. Indeed, in this group, the incidence of silent ischaemia did not differ from that of the normotensive group.

TABLE XVIII. *Number and incidence of silent ischaemia (SI) in the normotensive and hypertensive patients.* **$P < 0.01$

	No. with SI	Incidence (%)
Normotensive ($n = 80$)	11	13.8
Hypertensive ($n = 76$)	14	18.4
Good control ($n = 59$)	5	8.5
Poor control ($n = 9$)	5	55.6**
Incidental ($n = 8$)	4	50.0**

In conclusion, both incidental and poorly controlled hypertension are associated with silent ischaemia in a sample of elective surgical patients more than 40 years of age. Successful treatment of hypertension reduces the rate of silent ischaemia to almost the same as that in normotensive patients.

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POSTDURAL PUNCTURE HEADACHE IN UROLOGICAL SURGERY: AN EVALUATION OF THE ATRAUMATIC SPINAL NEEDLE

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Postdural puncture headache is a recognized complication of spinal anaesthesia. Its incidence and the influence of needle size and type have been studied extensively in the obstetric population. Spinal anaesthesia is used widely in our hospital for urological procedures such as transurethral resection of tumour (TURT) and of prostate (TURP). In a recent survey of 100 spinal anaesthetics, performed using a 26-gauge Quincke tip "Yale" needle, 24 % of patients reported a headache which had characteristics associated with dural puncture; 62 % of these were described as moderate or severe and lasted between 12 and 24 h [1].

After local Research Ethics Committee approval, we studied the effect of the introduction of a Sprotte 24-gauge needle on the incidence of postdural puncture headache. One hundred patients undergoing TURP or TURT who had been selected by their anaesthetist for spinal anaesthesia gave informed consent to the trial. Patients were allocated randomly to receive spinal anaesthesia using either a 26-gauge Quincke point Yale needle (group 1) or a 24-gauge atraumatic Sprotte needle (group 2). No attempt was made to standardize the anaesthetic technique. The anaesthetist recorded the number of attempts required and the eventual success or failure of the technique. All patients were visited within 48 h of their operation by an investigator who was unaware of the needle type used. Specific enquiry was made concerning the occurrence and duration of postoperative headache, characteristic of dural puncture. Severity of headache was graded as slight, moderate or severe using the criteria of Cesarini and colleagues [2].

All subjects were male and the groups were matched for age (median 70 yr (range 46–86 yr)). Postdural puncture headache occurred in 30 % of patients in group 1; 47 % were described as moderate or severe. Only 6 % of patients in group 2 reported a postdural puncture headache ($P < 0.005$; chi-square test) all of which were described as slight (table XIX). The incidence of multiple attempts at dural puncture was lesser with the Sprotte needle (28 % in group 1, 16 % in group 2) ($P < 0.05$; chi-square test). The treatment failed in two patients in group 1 and five in group 2.

We conclude that postdural puncture headache is a common problem in the elderly urological patient and that the incidence is reduced significantly by the use of an atraumatic spinal needle. Multiple attempts at dural puncture were also reduced significantly.

TABLE XIX. *Severity of postdural puncture headache and numbers of multiple attempts at dural puncture with the 26-gauge Yale and 24-gauge Sprotte spinal needles*

	> 1 attempt	Headache severity (No.)			
		None	Slight	Moderate	Severe
Yale	14	35	8	5	2
Sprotte	8	47	3	0	0

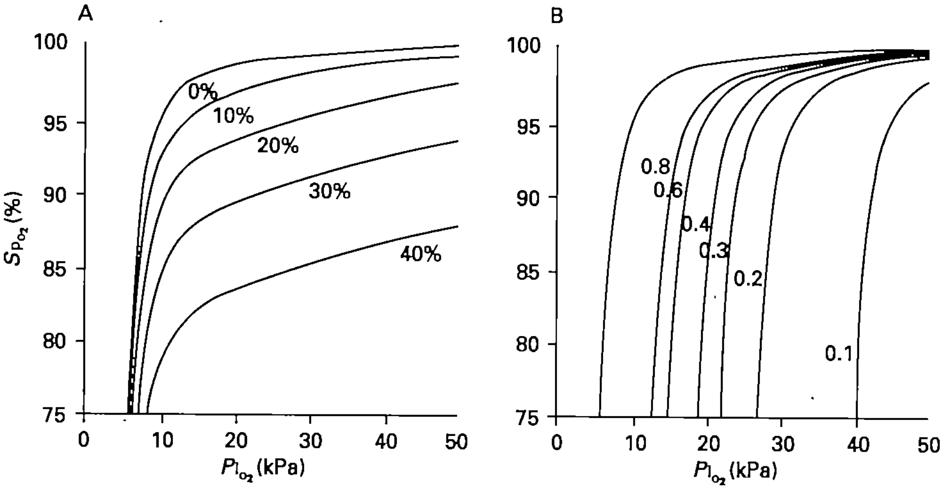

FIG. 7. Inspired oxygen (P_{IO_2}) *vs* arterial oxygen saturation (S_{pO_2}) for (A) a wide range of values of shunt and (B) a range of $\dot{V}/\dot{Q}$ values.

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DERIVATION OF $\dot{V}/\dot{Q}$ FROM THE POSITION OF THE P_{IO_2} *VS* S_{pO_2} CURVE

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We have shown previously [1] that after general anaesthesia there is a shift to the right of the P_{IO_2} versus S_{pO_2} curve. The mechanism for the shift was unexplained and it was assumed to be a function of maldistribution of ventilation to perfusion ($\dot{V}/\dot{Q}$) rather than shunt. The distinction between the effects of shunt and $\dot{V}/\dot{Q}$ can be made using the multiple inert gas clearance method [2]. This is a difficult, invasive and technically demanding technique available only in a few research laboratories. We present a method where shunt and $\dot{V}/\dot{Q}$ can be derived non-invasively using measurements of inspired oxygen (P_{IO_2}) and arterial oxygen saturation (S_{pO_2} or S_{aO_2}).

Plots of P_{IO_2} *vs* S_{pO_2} were constructed using $\dot{Q}s/\dot{Q}t = Cc_{O_2} - Ca_{O_2}/Cc_{O_2} - C\bar{v}_{O_2}$, for a wide range of values of shunt (shunt isopleths) (fig. 7A). Using the Rahn and Fenn [3] graphical method for deriving $\dot{V}/\dot{Q}$, a series of $\dot{V}/\dot{Q}$ lines were constructed, the mixed venous point being constant but the P_{IO_2} varied from 21 to 50 kPa. A series of gas exchange R lines corresponding to a range of $\dot{V}/\dot{Q}$ values were constructed and from these lines a P_{IO_2} *vs* S_{pO_2} plot calculated for each value of $\dot{V}/\dot{Q}$ (fig. 7B) using a standard oxygen dissociation curve. Figure 7B shows the relationship between $\dot{V}/\dot{Q}$ and the curve position as measured by the lateral shift in kPa.

This approach shows that shunt (fig. 7A) moves the P_{IO_2} *vs* S_{pO_2} curve downwards and a diminishing $\dot{V}/\dot{Q}$ (fig. 7B) moves the curve to the right.

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CORRESPONDENCE

RETROGRADE INTUBATION USING THE SUBCRICOID REGION

Sir,—Dr Shantha recommends puncture of the cricotracheal instead of the cricothyroid ligament for retrograde intubation, because he believes that bleeding complications may be avoided and the risks of subglottic oedema and stenosis decreased [1]. However, to our knowledge, these arguments have not yet been substantiated. In the presence of venous stasis, a frequent occurrence with difficult intubation, the incidence of bleeding at the puncture site is probably at least as frequent. Moreover, the subcricoid approach is more difficult or impossible in the obese, in the presence of goitre or cervical haematoma.

In common with Dr Shantha, we recommend the subcricoid route but for the following reasons: it has the greatest success rate with the guide threaded through the Murphy eye; it carries the smallest risk of damage to a vocal cord by the needle or the catheter; and it allows a deeper tracheal penetration of the tracheal tube, thus decreasing the risk of accidental extubation at catheter removal. These data were obtained during a study by our group published in a French journal of anaesthesia in 1989 [2].

Our study included 77 cadavers of adults who had died less than 4 h previously and were devoid of morphological causes of difficult intubation. They were allocated randomly to four groups depending on the site of puncture (cricothyroid ligament = groups 1 and 2; cricotracheal ligament = groups 3 and 4) and the mode of catheter insertion (complete tracheal tube lumen catheterization = groups 1 and 3; only Murphy eye catheterization = groups 2 and 4). We used a Tuohy needle (17-gauge) with the corresponding extradural catheter. After the intubating manoeuvre, the airways were dissected and checked for local damage. The results (table I) demonstrated a success rate of 100 % in group 4. This was significantly different from those in other groups. Damage to a vocal cord occurred only with the cricothyroid route (8 % of cases).

TABLE I. *Number of successful retrograde intubations (total number and number at first attempt) and of cases of vocal cord damage, in 77 cadavers allocated to four groups with regard to site of puncture and mode of catheter insertion into the tracheal tube (either through the lumen (ET) or only through the Murphy eye)*

		Successful intubations		
	n	Total	First attempt	Vocal cord damage
Group 1 Cricothyroid puncture+ET	17	5	4	3
Group 2 Cricothyroid puncture+Murphy eye	20	15	11	
Group 3 Cricotracheal puncture+ET	20	14	13	0
Group 4 Cricotracheal puncture+Murphy eye	20	20	17	
Total	77	54	45	3

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Sir,—We have been using retrograde methods for almost 25 yr. We have seen almost every complication as reported in the article [1]. Haematoma is not an uncommon complication. There are reports of intratracheal bleeding when this route is used for aspiration, resulting in serious, life-threatening complications [2–5]. Of course, I agree with Dr Lleu and his group that bleeding into the trachea is rare, but haematoma and formation of subcutaneous emphysema, although perhaps unnoticed, are not uncommon.

We did have a case of massive goitre. All methods of intubation, including a fibreoptic bronchoscope, failed; the cricothyroid membrane was exposed by a small incision, enlarged blood vessels on the membrane were tied and a retrograde method was used successfully to intubate, avoiding the necessity for tracheostomy. The subcricoid region is difficult to use if there is a mass goitre.

We had cases of a prolonged change in voice and feeling of soreness after a somewhat traumatic retrograde intubation using the cricothyroid region. This was not the case when the subcricoid region was used.

I am happy to note that cadaver studies do agree with our and other reports of ease of intubating using the subcricoid region [1, 6, 7]. We have used the subcricoid retrograde method for difficult intubations successfully since 1982, with minimal complications [1]. I am sure that the incidence of damage to vocal cords and subglottic oedema may be much greater than 8 % if intubation is performed on live patients using the cricothyroid region.

I conclude that, when all other methods to intubate the larynx fail, the subcricoid retrograde method is the best and least complex available.

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VENTILATORY EFFECTS OF LAPAROSCOPY UNDER GENERAL ANAESTHESIA

Sir,—The study by Puri and Singh [1] is well designed and a valuable contribution to our knowledge of respiratory physiology. However, we wish to make the following comments on this subject, as we were involved in previous studies utilizing similar methodology in pregnant subjects [2–4].

The haemodynamic changes during laparoscopy also are important in the interpretation of arterial to end-tidal differences in carbon dioxide tension ($Pa_{CO_2}-P\bar{E}'_{CO_2}$) values and the relevant data have not been presented. Studies have shown that laparoscopy may be associated with increases in cardiac output and arterial pressure [5, 6], and changes in cardiovascular dynamics could result in changes in $\dot{V}/\dot{Q}$ state in the lung and hence in $(Pa_{CO_2}-PE'_{CO_2})$.

Second, in the absence of capnographic recordings, the authors could have estimated the components of physiological deadspace using traditional formulae [4, 7] instead of speculating that anatomical deadspace may have decreased during laparoscopy.

Finally, negative values of $(Pa_{CO_2}-PE'_{CO_2})$ have been observed during anaesthesia in pregnant subjects (50%), in infants (50%) and in patients after cardiac bypass surgery (8.1%) [8]. The increased cardiac output and increased carbon dioxide production, reduced FRC and low compliance are factors that have been implicated in the production of negative values. Therefore, one would be interested to know the incidence of negative values, particularly during stage II of Puri and Singh's study where, after insufflation of carbon dioxide into the peritoneum, the subjects may resemble the pregnant in some features, namely reduced FRC, low compliance and increased carbon dioxide production.

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Sir,—Although $(Pa_{CO_2}-PE'_{CO_2})$ in individual patients changed at different stages of laparoscopy, there were no overall mean changes in $(Pa_{CO_2}-PE'_{CO_2})$ at various stages of laparoscopy studied (indicated in table I of our paper [1]). Some of these individual … from the changes in

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EUROPEAN STANDARDIZATION COMMITTEE ON ANAESTHETIC EQUIPMENT

Sir,—Our publication [1] on fresh gas utilization of eight circle systems was one of the first testing the new European CEN standard. Dr Greenbaum's statement [2] that our reference to the draft document of the CEN/TC215 proposal was not authorized, is incorrect. As stated in the introduction of the proposal, the standard may be quoted with the approval of the Convenor of the working group or the Chairman. Approval for our publication was obtained from both before submitting the manuscript (the Chairmanship of the Technical Committee has changed in the meantime).

As already mentioned, our publication describes a testing procedure under well defined circumstances and nothing else. It does not set performance limits. I have no knowledge of any other type testing standard which reliably evaluates the efficiency of anaesthesia systems. It is left to the member states of CEN to accept, alter or omit it completely from the final document.

We consider it as essential that standards are discussed and evaluated by an international readership of various journals before they become accepted standards. In the past, too many standards have been designed in theory only and therefore tend to lack data for their applicability in clinical practice. By testing the standards we would hope, therefore to make a contribution towards avoiding such problems in the future.

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RADIOIMMUNOASSAY TESTS AND ANAPHYLAXIS

Sir,—Dr Fisher's letter [1] has raised doubts about the ability of the commercial paper radioallergosorbent tests (RAST) to categorize correctly patients who have suffered anaphylactic reactions when the commercial test is compared with their own laboratory methods. The documentation of false negatives with the commercial RAST is an important finding and suggests that diagnostic skin testing [2] also should be performed for appropriate drugs, particular if sera from known RAST-positive patients are not available to validate the commercial tests.

Another area of concern is the use of these RAST for screening before anaesthesia [3]. Here, because larger numbers of patients would be tested, the false positive rate, in addition to the false negative rate, would be important [4]. After a fatality in Aberdeen … methonium-induced anaphylaxis, a prospec-

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RESPIRATORY DEPRESSION AFTER EXTRADURAL FENTANYL

Sir,—I read with interest the case report by Brockway and colleagues [1] and the article by Noble and colleagues [2] on respiratory depression after extradural fentanyl. In view of the apparent rarity of this complication, I wish to report a similar case which I encountered recently.

A healthy, 30-yr-old patient (gravida 1) presented for elective Caesarean section because of uterine abnormality. The current pregnancy had been uneventful. Preoperative examination was unremarkable (weight 56.0 kg, height 1.54 m). She was premedicated with two doses of oral ranitidine 150 mg and sodium citrate 30 ml before surgery.

Before an extradural block was induced, the patient received Ringer's lactate solution 1 litre. Patient monitoring included ECG, non-invasive arterial pressure measurement (Dinamap) and pulse oximetry (Nellcor). With the patient in the left lateral position, the L2–3 extradural space was identified with a 16-gauge Tuohy needle, using loss of resistance to saline. An extradural catheter was passed 4 cm cephalad and 0.5% bupivacaine 3 ml was injected through a Millipore filter as a test dose. After 5 min, and with no evidence of intrathecal or intravascular administration, 0.5% bupivacaine 7 ml was injected in divided doses over 5 min with the patient positioned with the pelvis tilted 15° to the left using a wedge under the right hip. An additional 0.5% bupivacaine 8 ml with fentanyl 100 µg was then injected incrementally over 10 min.

Bilateral sensory block to T6 was obtained after 5 min. Maximum block height was obtained at 10 min: bilateral T2. The motor block was assessed using a Bromage scale: the patient was just able to flex both knees and was graded 1. There was a decrease in systolic arterial pressure from 96 to 87 mm Hg and heart rate decreased from 56 beat min^{-1} to 51 beat min^{-1}. Ephedrine 8 mg and atropine 0.3 mg were given i.v. Thereafter, arterial pressure and heart rate returned to normal.

Surgery was commenced 30 min after completion of the injection. Before delivery, the mother received oxygen 3 litre min^{-1} via an intranasal cannula and the pulse oximeter showed 100% saturation. Just before the start of surgery, the patient said that she felt drowsy and complained of persistent nausea; she was given metoclopramide 10 mg i.v. A healthy child was delivered with an Apgar score of 9 at 1 min; syntocinon 10 iu was given i.v. The anaesthesia and the surgery continued smoothly until, 80 min after the initial injection of bupivacaine and fentanyl, the patient became increasingly drowsy and her ventilatory frequency decreased from 12 to 3 b.p.m. and Sp_{O_2} had decreased from 96% to 86% (breathing air). Her heart rate remained unchanged. Administration of oxygen 3 litre min^{-1} was recommenced via an intranasal cannula and on command she took deep breaths and Sp_{O_2} improved. The patient's ventilatory frequency repeatedly decreased to 2–3 b.p.m. with decreases in saturation to between 86% and 90% and on each occasion she was instructed to take deep breaths. After 10 min, when it had become obvious that the increasing drowsiness with ventilatory frequency of 2–3 b.p.m. was persisting, naloxone 0.2 mg i.v. was administered. Approximately 30 s later, the patient became alert and the ventilatory frequency increased to 16 b.p.m. and she was able to maintain Sp_{O_2} greater than 96%. Five minutes later, she was again drowsy but responded to verbal encouragement to awaken and breathe deeply and was able to maintain her oxygen saturation greater than 96%. Over the next 20 min the patient's condition improve without further administration of naloxone. After the operatio the patient was observed and oxygen saturation was monitore continuously for a period of 3 h, with no further episode o desaturation. She was then returned subsequently to the postnatal ward.

It was considered that the respiratory depression in this patient was probably caused by the larger dose of fentanyl being administered, enhancing rostral spread via a direct perimedullary vascular channel [3].

This case further strengthens the importance of continuous monitoring of patients for an adequate period after extradural fentanyl and highlights the need to limit extradural administration of fentanyl to small doses.

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A PUNCTURE TECHNIQUE FOR CONTINUOUS SUBARACHNOID BLOCK

Sir,—Continuous spinal anaesthesia is a well-described technique [1], but the occurrence of postdural puncture headache (PDPH) is the main factor limiting its popularity. Loss of CSF and its relation to intraspinal compliance is one of the causative factors of PDPH [2]. The variability of CSF loss during continuous spinal anaesthesia is a matter of controversy [3, 4]. However, in spite of the many publications on the technique, there is little information on the technical implementation of the procedure [1, 5].

We have used the technique of continuous spinal anaesthesia since January 1990. Perifix extradural equipment (Braun, Germany) is used with a Tuohy 18-gauge needle and 20-gauge polyamide multiperforated catheter, as part of a technique which detects the subarachnoid space while minimizing initial CSF loss.

Regardless of patient position, the needle bevel is introduced parallel to the ligamentous and dural fibres. The extradural space is located initially by loss of resistance (air) or using an electronic detector (Episensor, Palex, Spain) [6]. The detection system is then removed, and a catheter threading aid is fitted, where the catheter tip emerges from the diaphragm end of a transparent blind hub. The total unit is introduced smoothly with the non-dominant hand. At the moment when the hub fills with CSF, the needle is rotated with the outlet orifice cephalad; the dominant hand is then used to advance the catheter inside the needle to 3–5 cm within the subarachnoid space.

During conventional dural puncture when the needle stylet is removed, an uncontrolled loss of CSF occurs—particularly when larger needles are used, even when the stylet is replaced quickly by the catheter threading aid. With our system, the initial loss of CSF is limited to the needle hub volume (approximately 0.12 ml for an 18-gauge needle),—a minimum, controllable volume that is always predictable. The catheter within the needle hub acts as a plug against the loss of CSF and facilitates easy and rapid introduction into the subarachnoid space.

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BACTERIAL OVERGROWTH AND GASTRIC DYSFUNCTION

Sir,—The issue of bacterial overgrowth in patients undergoing mechanical ventilation of the lungs, raised by Dr T. Inglis and colleagues [1], is important because of the serious consequences of nosocomial infections in patients in the intensive care unit (ICU). As the relationship between gastric acidity, bacterial growth and nosocomial infections remains unclear, the authors' assumption that factors other than acidity are likely to play an important role in gastric bacterial overgrowth is justified.

The interpretation of the data from this study should, however, take into account the following points. Random, widely-spaced sampling of gastric juice for bacterial count and pH does not allow correlations on the effect of pH on bacterial growth, as almost all bacteria commonly implicated in nosocomial pneumonia in patients undergoing artificial ventilation are killed after 10 min of exposure to gastric juice at a pH < 4, with virtually no regrowth within 24 h [2]. Because brief fluctuations in pH are not reflected in sporadic pH measurements, which constitute a mean pH, the results based on such techniques must be interpreted with great caution. This applies especially to evaluation of H_2-receptor antagonist treatment in patients in the ICU, in whom a consistent increase in pH to > 4 is achieved rarely, and in whom recurring episodes of acidity occur [3–5]. Consequently, to examine the effect of pH on bacterial growth, frequent or, preferably, continuous measurements of pH should be performed.

In the study by Inglis and colleagues [1], six patients were given sucralfate, which has a bactericidal action independent of pH [2, 6], and these patients should be excluded from the analysis of the effect of pH on bacterial growth.

It would be interesting to have some more information on the bacterial strains cultured, as the susceptibility to acid may vary with individual bacterial properties, such as resistance to antibiotics [1]. Did insertion of the nasogastric tube lead to contamination of the gastric specimens with oral flora in patients who were hypoacidic?

The increased duodenogastric reflux documented in these patients indicates post-traumatic and postoperative intestinal motility disorders, which could well predispose to gastric stasis and bacterial regurgitation from the lower intestine. More specifically-designed studies seem to be necessary to elucidate the exact relationship between gastric pH and bacterial growth in ICU patients.

C. H. Wilder-Smith
Berne, Switzerland

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Sir,—The author of this letter made five points which I should like to address.

Work we have performed [unpublished] also has indicated that the pH of gastric specimens fluctuates frequently in some patients undergoing artificial ventilation of the lungs; however, we were unable to sample more frequently on account of the volume of gastric aspirate required. If we had done so, we would not have been able to discard the nasogastric tube deadspace volume and still have a sample sufficient for analysis. Moreover, Dr Wilder-Smith claims that almost all bacteria in the stomach will be eradicated by very low pH within 10 min. Work in several different centres indicates that small numbers of bacteria exposed to low pH for up to several hours remain viable, and may regrow after a lag phase. As the relationship between bacterial death and exposure to acid is a complex one, the only practical approach to use is to measure the organisms present and the pH in the same sample, and to try to avoid speculation about fluctuations of each variable during the intervening period.

The author refers to two publications claiming antibiotic activity for sucralfate. Both of these studies used non-standard bacteriological methods. The claim for antibacterial activity for this compound is therefore still controversial. We are investigating this compound currently using conventional antimicrobial analyses, and although our preliminary results support the presence of some effect, this is variable and may depend on different local factors, including: species of bacteria, mucosal binding, local pH and the presence of bile acids. Therefore, it is not possible to anticipate the activity of sucralfate on organisms isolated from gastric aspirate specimens without measurement of these, as yet, unevaluated variables.

The list of bacterial species cultured from samples in this study is shown in table I.

Table I. *Organisms isolated from gastric aspirates*

Species	No. of patients colonized
Gram-negative bacilli	
E. coli	2
Pseudomonas fluorescens	2
Klebsiella pneumoniae	1
Klebsiella oxytoca	1
Serratia marcescens	1
Serratia liquefaciens	1
Proteus mirabilis	1
Enterobacter agglomerans	1
Other	
Gram-positive cocci	10
Streptococcus spp.	7
Staphylococcus spp.	3
Gram-negative cocci	3
Gram-positive bacilli	1
Yeast	4

It is true that insertion of a nasogastric tube may introduce bacteria from the bronchial cavity or oropharynx into the stomach, which subsequently colonize the gastric lumen. However, this is an issue of secondary importance, as all these patients had a nasogastric tube, and it does not account for the apparent relationship between gastroduodenal reflux and bacterial overgrowth.

The author states that further studies are required and is, no doubt, keen to conduct one himself! In our publication we have taken great care to present our data as a preliminary report and have sought to draw only tentative conclusions. A follow-up study addressing the relationship between gastroduodenal dysfunction and bacterial colonization of the ventilated airway in a larger number of patients is nearing completion. Although the statistical analysis has yet to be confirmed, preliminary results appear to support the conclusions of our pilot study and have important implications for the prevention of ventilator associated pneumonia.

T. Inglis
Leeds

British Journal of Anaesthesia 1992; **69**: 546–548

BOOK REVIEWS

Emergency Medicine and the Anaesthetist (*Baillière's Clinical Anaesthesiology* series). Edited by H. H. Delooz. Published (1992) by Baillière-Tindall, London. Pp. 212; indexed. Price £27.50.

This is the latest addition to the *Clinical Anaesthesiology* series on specialized topics, published four times a year. In common with its predecessors, it has several contributors from Europe, America, and the U.K.

The risks of this format are undue repetition and variations in style. Here, these problems have been avoided, and the Guest Editor has managed to assemble a series of monographs of astonishing diversity. Practical descriptions of resuscitation and of anaesthesia for traumatized patients are accompanied by scholarly accounts of oxygen transport and the pathophysiology of pain. Of especial value are the several chapters dealing with the audit and management aspects of emergency medicine including, in the editor's own introductory chapter, emphasis on the need for a multidisciplinary approach to care of the patient. I particularly liked the chapter on trauma patient scoring, in which the several systems available are analysed carefully for what they are intended to assess.

It is unusual in a book on emergency medicine to find a whole chapter on the care of the dying, and the evocative title made me turn to it before assessing the rest of the book. I found a deeply philosophical account of the ethical complexities of death. It makes fascinating reading, but whether or not it is appropriate to a book of this nature is debatable. That said, I would recommend this thought-provoking chapter to all who have care of the dying.

This is an excellent book which can be recommended, not only to anaesthetists, but to all doctors (and other health care professionals) who are involved in emergency medicine. Specialists in the field should read it all; others, including candidates for the anaesthetic Fellowships, can be more selective. This is not difficult, as the chapter titles are very descriptive and the index is comprehensive.

J. N. Horton

MCQ for the Higher Examinations in Clinical Pharmacology. By G. McCarthy and R. K. Mirakhur. Published by Edward Arnold, Sevenoaks. Pp. 127; indexed. Price £9.99.

One disappointing feature of modern medical education and examinations is the reduction in dependence on the essay. Medical students and young doctors write few sentences—whole paragraphs are very rare. It has become accepted that factual knowledge will be assessed using the so-called multiple choice question (MCQ). This type of interrogation has proliferated in the examinations of the colleges in the U.K. While the Colleges of Physicians of the U.K. have chosen to publish examples of their questions as a guide to candidates at least 20 years ago, other colleges and faculties have been less forthcoming.

The present offering has been composed by a senior lecturer in Anaesthesia (who is also an examiner in Pharmacology for the higher examination in Anaesthesia) and a research fellow from the same University Department in Belfast. The book consists of 13 chapters of questions on the verso with answers and explanations on the corresponding recto. The 13 chapters of questions include the cardiovascular system, respiratory system, anaesthesia, local analgesia, the gut, anticholinergic drugs, the central nervous system, antibiotics, endocrinology, the blood, general pharmacology and statistics. The fourteenth chapter is a list of 14 books published between 1980 and 1981, considered by the authors to be useful reading.

The authors themselves describe the aim of the book—to let the student test what he already knows and also to point out the areas in which knowledge is lacking. The target audience includes "anaesthetists, pharmacologists and doctors in a wide range of medical disciplines." In spite of this aim and the implication of the title, the book is intended for anaesthetic trainees. I cannot imagine any other group using it in significant numbers. There are two line drawings (a dose–response curve and a barbiturate nucleus) and no references whatsoever. If one chose to do so, one could criticize some questions, but it is extremely difficult to write good, non-ambiguous, questions. The great majority of stems consists of one word (usually a drug name) and this may not reflect actual questions in use in examinations. Almost 20% of the questions concern anaesthesia or analgesia.

There is nothing wrong with this book. The format is not original and one must assume that someone buys such texts. It may test the knowledge of the reader if used honestly and it may be a help to organize personal study. The authors admit that it is not comprehensive and therein lies the criticism of the approach to learning epitomized by publications such as this. The student who tries to cut corners and is short of time would be better to read a real textbook of Pharmacology. The student who has studied conscientiously and read recognized texts may not benefit significantly from using this book.

W. S. Nimmo

Clinical Practice of Regional Anesthesia. Edited by P. Prithvi Raj. Published by Churchill Livingstone, New York. Pp. 543; indexed; illustrated. Price £70.00.

This book started life in 1985 as the *Handbook of Regional Anesthesia*. It has been expanded and updated, and is now a textbook in all but name. There are 27 authors, five of whom are based in Europe and the remainder in North America. First impressions are favourable. The hard cover looks and feels good, the quality of the paper and print is excellent, the line drawings are clear, the occasional use of a single colour to give them emphasis is effective, and the book contains a mass of information.

However, the transition from handbook to textbook has been neither easy nor entirely successful. The editor has had to decide if his authors should remain free-range birds and be allowed to peck on each other's territory, or if he should clip their wings and coop them up. The latter approach would have produced a more uniform literary style, minimized repetition and shortened the book by about 100 pages. Dr Raj has opted for the free-range. The result is that, although enthusiasm and commitment are apparent throughout, some authors have been allowed to indulge their idiosyncrasies and ride their hobby horses, so inspiration and irritation are present in almost equal measure. For example, in the chapter on monitoring and equipment, fluoroscopy as an adjunct to regional anaesthesia is given almost as much space as the nerve stimulator, and we are even treated to a dissertation on dark adaptation and the function of rods and cones. Most anaesthetists would benefit from reading the comprehensive chapter on preoperative evaluation, but only a fraction of it is directly relevant to regional anaesthesia. Much of the writing is verbose, but the chapters comparing regional and general anaesthesia and discussing endocrine and metabolic effects are concise and lucid. Tables are often too big and complicated because authors, in their anxiety to miss out nothing, have packed them with too much information. The black and white photographs are of poor quality and some, such as those showing an anaesthetic machine cluttered with monitors, do not add to the text.

The lay-out of the book has obviously posed problems for the editor. There are four main sections: general aspects; equipment, monitoring and drugs; regional anaesthesia for surgery; and regional anaesthesia for specific situations. This format has the advantage that it lends itself to a problem-solving approach, but it encourages repetition, and one does indeed find that information given in one section is repeated elsewhere. For example, there is a section on children in an otherwise good chapter on post-operative pain in adults, despite the fact that the next chapter, written by different authors, is devoted specifically to post-operative pain in children. The aforementioned section on nerve stimulators seriously encroaches on the very adequate chapter which deals exclusively with this subject. The decision to describe the monitoring and equipment required for each block ("a functioning intravenous catheter should be started...") inevitably results in repetition. The section on brachial plexus block ends with a paragraph on complications, even though these are mentioned in each of the sub-sections on interscalene, supraclavicular and infraclavicular block. Furthermore, repetition is not confined to the text. Figure 11.20, showing a patient positioned for intercostal block, first appears inappropriately in the chapter on the rationale and choice of regional anaesthesia for surgical procedures. It finds its correct place 80 pages later as Figure 12.26, now illustrating interpleural block in the chapter on techniques of regional anaesthesia in adults, and it makes a farewell appearance, as Figure 17.10, in a wayward chapter on trauma and the intensive care unit, in which regional anaesthesia gets a passing mention.

Who should buy this book, and is it worth the money? Dr Raj states that it is aimed at all clinicians with an interest in regional anaesthesia, and there is no doubt that it is a significant addition to the literature because it occupies a place midway between the large, multi-volume texts and the smaller, more didactic primers. For this reason, it deserves to be in the Anaesthetic Department library. The individual anaesthetist, however, will probably be unwilling to pay £70 for a book of 543 pages, of which only 443 contain material relevant to the subject and stated once only.

E. N. Armitage

Maternal Mortality—The Way Forward. Some Implications of the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–87. Edited by N. Patel. Published by The Royal College of Obstetricians and Gynaecologists, London. Pp. 196; illustrated. Price £7.00.

This book is an account of the proceedings of a Postgraduate Meeting held in the Royal College of Obstetricians and Gynaecologists in 1992. It consists of an analysis and management of the major causes of maternal deaths and is based on the Confidential Maternal Mortality Report. Thus the topics covered are pre-eclampsia, eclampsia, haemorrhage and thromboembolic disease. The contributors are well known and write clearly and with brevity. Anaesthetic input is limited to one chapter on haemorrhage by Professor Rosen. There is, disappointingly, no chapter on acid aspiration. This is unfortunate, as there can be little doubt that the introduction of the H_2 antagonists and the abandonment of magnesium trisilicate have had a major and beneficial effect; it is only by enthusiastic proselytizing that the impetus can be maintained, and here an opportunity has been missed.

This book should be on the shelf of every obstetric and anaesthetic library, and at its bargain price every obstetric anaesthetist should have a copy. Despite that recommendation, it is a provocative book which encourages thought. No one will agree with all of it, but it is warmly recommended.

J. Thorburn

Critical Care Toxicology (Contemporary Management in Critical Care series). Edited by R. S. Hoffman and L. R. Goldfrank. Published by Churchill Livingstone, New York. Pp. 256; indexed; illustrated. Price £22.50.

This latest volume in the *Contemporary Management in Critical Care* series consists of 10 articles on varying aspects of acute poisoning, written in the main by experts in toxicology and emergency medicine. It is neither a comprehensive reference book nor a management handbook, but rather an update on the subject.

Its approach is to address several issues of relevance to the general management of acute poisoning, rather than to deal with individual drugs. Hence there are chapters on oral activated charcoal therapy, extracorporeal drug removal, sodium bicarbonate therapy, *etc.* It is in its discussion of these therapies and their rationale and indications in different intoxications that this book is most useful. Nevertheless, it is unfortunate that information on a specific drug, which is scattered through many chapters, could not have been brought together, if only in an Appendix, to provide an updated reference for treatment of a specific drug overdose. For example, to update oneself on the management of a tricyclic overdose, one has to consult the index and then head for five different chapters to gain information on oral activated charcoal, extracorporeal removal, bicarbonate therapy and treatment of haemodynamic complications. Furthermore, paracetamol is barely described, the only mention being the interactions between N-acetyl cysteine and oral activated charcoal.

The excellent chapter on smoke inhalation manages successfully to combine the general principles with the specific management problems of individual toxic gases. It is a pity the same could not have been achieved elsewhere.

For intensive care clinicians, it is sad that the chapter on intensive care management is at such a basic level. With the exception of two tables listing criteria for admission to the ICU, there are too many vague platitudes, even though there is some very useful information about various aspects of different poisons. The book's weakness on intensive care is again apparent in the chapter on haemodynamic compromise. There is insufficient detail on haemodynamic monitoring. The authors tell us repeatedly where dopamine may not be useful, but devote less space to the alternatives. There is also no discussion of the choice of fluid for resuscitation.

The use of brief summaries in the broad margins to emphasize the main points in the text is only a qualified success: much space is wasted, and many of the points are not very valuable. It would have been much more useful to have interrupted the text with more headings and tables.

There is an abundance of useful references, and a reasonable index. Appendices dealing with the particular drugs would have been helpful. Unfortunately, this book is often long-winded, the useful information contained is often hard to find, and treatment guidelines are not specific enough. The authors do recognize the limitations, by referring the reader to major texts for detailed management advice.

This book will prove useful for a reader wishing to gain up-to-date information on the use of specific treatments in drug overdose. It will not serve, however, as an ICU treatment reference, and its usefulness will therefore be considerably limited.

I. S. Grant

Manual of Obstetric Anesthesia, 2nd Edn. Edited by G. W. Ostheimer. Published (paperback) by Churchill Livingstone, New York. Pp. 451; indexed; illustrated. Price £39.00.

This edition of *Manual of Obstetric Anesthesia* is excellent. There are 69 contributors who obviously have been given a tight brief. Each contribution is in a similar format, punchy and didactic without being dictatorial. It is suitable for trainee anaesthetists in addition to established consultants and will be useful for reference when a quick answer is required.

The book is a mine of information and a magnificent source of reference, as are all North American textbooks. One wonders if U.K. consultant job plans will ever contain a weekday in the medical library, although one could arrange a CD-rom terminal at home for Sundays.

There are 11 main sections, each with appropriate subdivisions. The changing nature of obstetric anaesthesia is reflected by the large section on The High Risk Parturient which includes congenital heart disease, myocardial infarction, transplantation, autoimmune disease, drug addiction and acquired immunodeficiency, all of which are increasingly relevant in U.K. practice.

Obstetric anaesthesia is a consumer orientated specialty. Obstetric anaesthetists have had to take cognisance of the wishes of patients, probably more than any other specialty. The book reflects this, with sections on Non-Pharmacologic Pain Relief, Medicolegal Aspects of Obstetric Anesthesia and Neurologic Sequelae of Childbirth and Regional Anesthesia. The management of the Jehovah's Witness is discussed in detail, with appropriate quotations from *The Bible*. In the section on Altered Coagulation, the author quite rightly emphasizes the importance of performing a bleeding time before inducing an extradural block.

The last section is on Education, Organization and Standards. Education should be read by all Part 3 examiners; Organization by obstetricians, midwives, anaesthetists and managers; Standards by all Purchasing Authorities, especially since publication of the House of Commons Health Committee's Second Report on Maternity Services. They should also read the section on Maternal and Perinatal Mortality before deciding the proportions of community, general practitioner and consultant obstetric care to purchase.

The index is comprehensive. The text is so readable that one does not miss the paucity of diagrams. The quality of the paper and the type setting contribute to the ease of reading, even by artificial light! The book is a paperback, presumably to reduce costs. This is a pity because, with more than 400 pages, it will quickly become dog-eared.

This book merits a place in every hospital library and obstetric anaesthetic department. The reviewer will purchase a personal copy, not only for frequent perusal, but to keep by the telephone for quick reference.

R. Macdonald

The Management of Acute Pain. By G. Park and B. Fulton. Published by Oxford University Press, Oxford. Pp. 163; indexed; illustrated. Price £14.95.

The first recommendation of the Joint College Report on Postoperative Pain was to improve the education of hospital staff looking after patients recovering from surgery. This book aims to provide practical guidance for those who have been traditionally responsible for the administration of drugs for acute pain relief—that is, junior medical and nursing staff.

The first quarter of the book is a theoretical description of the importance of treating pain, pain pathways, psychological aspects of pain, principles of drug administration and opioid pharmacology. The opening chapter of this section on why pain control is a problem is a clear description of our failure to assess pain accurately and how the fear of side effects and addiction has limited the use of potent analgesic drugs. Unfortunately, the section on pain assessment is extremely brief and does not emphasize the importance of pain assessment on movement or the integration of pain scoring into the nursing process. Conversely, the lengthy chapters on pain pathways and pharmacology may be too detailed for the target audience.

The practical section of the book addresses the use of different forms of analgesia, ranging from opioids by the i.m., i.v. and intraspinal routes to local anaesthetic drugs and NSAID, in a variety of clinical situations. The strength of the book is that this section, which is easy to read and likely to be read, brings together a great deal of practical advice and guidance which the junior doctor or nurse would find valuable. However, although the authors achieve their objective of providing simple guidance for junior medical and nursing staff, this approach limits the usefulness of the book for the more experienced anaesthetist.

Topics which are not covered include the specific problem of nausea and vomiting with patient-controlled analgesia, opioid sparing techniques, pre-emptive analgesia and the use of mixtures of opioid and local anaesthetics via the extradural route. In addition, the contentious issues of the respiratory effects of analgesic techniques and the use of regional techniques in patients receiving subcutaneous heparin are dealt with very briefly.

R. G. Wheatley

The Critical Care Drug Handbook. By G. P. Zaloga. Published by Wolfe Publishing Ltd, London. Pp. 537; indexed; Price £18.00.

This handbook consists of three sections. The main body of the book is an alphabetical listing of drugs used in the critical care setting, with two smaller sections on problems and appendices.

The problem section provides a form of index, in that it takes a condition, such as bradycardia, and lists the relevant therapeutic agents which can be cross-referenced with the alphabetical listing. In the main section, each drug is dealt with under the following headings: trade name, drug action, indications, pharmacokinetics, drug preparations, dosage, drug interactions, monitoring and bibliography. The appendices contain information on several treatment regimens, for example prophylaxis for endocarditis.

There is much useful information in the handbook, but the paperback itself is flimsy and the reviewer's copy is already showing signs of wear. Unfortunately, it is difficult to see a place for this work in the British market as most of the information contained in the book is already in the *British National Formulary*.

G. W. Jones

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The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).

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"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

THE ERA OF RELAXANT ANAESTHESIA

This year we celebrate, with good cause, the 50th anniversary of the introduction of "curare" into anaesthesia by Griffiths and Johnson of Canada [1]; this was a momentous event, as time has shown, for anaesthetists, surgeons and patients. These workers used Intocostrin, a biologically standardized mixture of the alkaloids of *Chondrodendron tomentosum*, to facilitate relaxation during cyclopropane anaesthesia. A new era in our specialty had begun.

The state of anaesthesia 50 years ago was, by the standards of today, primitive. The volatile and gaseous agents then available were nitrous oxide, ether, chloroform, cyclopropane, ethylene (in U.S.A.) and trichloroethylene—nothing else. A barbiturate or thiobarbiturate was frequently used intermittently to maintain anaesthesia and rectal "basal narcosis" was popular. Local infiltration, some nerve blocks, spinal, caudal and, to a lesser extent, extradural analgesia were also available. It was with this armamentarium that the anaesthetist had to tackle major surgery.

This is not, perhaps, an inopportune time to outline the contribution made by a group of anaesthetists in Liverpool to the development of the use of relaxant drugs and of a safe anaesthetic regimen which could be used with them—the so-called "Liverpool Technique". This Liverpool School was responsible both for a new conceptualization of anaesthesia which centred on these drugs rather than regarding them as peripheral adjuvants, and for increasing their popularity and safety at a time when the realization of their importance and scope was developing very slowly.

Slow indeed, it was. In 1945, a year before the first paper on relaxants emanated from Liverpool, Griffiths, the founding father, clearly regarded the new agent as an adjuvant, to be used occasionally, perhaps once a week [2]. In 1952, when ideas in Liverpool had been largely crystallized, the over-all use of curare in the hospitals investigated by Beecher and Todd [3] was only 0.2% of patients anaesthetized. Cullen [4], a true pioneer with relaxants, was showing but a very restrained enthusiasm in 1946.

Much progress had been made by 1946, however. The virtues of curare in permitting the use of lighter planes of anaesthesia had been emphasized by Knight and Baird from the U.S.A., as early as 1944 [5]. The suggestion by Knight, also in 1944 [6], that in the pursuit of this end, incremental doses of relaxant should be given, rather than anaesthesia deepened, again indicated a shift of thought, from the use of curare merely as an adjuvant to the accordance to it of a more central role in technique.

In 1945, Waters [7] described the use of curare with nitrous oxide as the sole anaesthetic agent, but the dose used was small, a tracheal tube was not passed and no attempt was made to control ventilation.

Later, in 1946, Harroun, Beckert and Hathaway [8] administered curare in much larger doses (Intocostrin up to 200 mg; equivalent approximately to tubocurarine 30 mg)—the acceptable dose in some hands appeared to be increasing. These workers inserted a tracheal tube, and then continued to control ventilation until spontaneous breathing returned. Nitrous oxide was the sole anaesthetic, with, if required, incremental doses of pethidine—a drug later to be strongly advocated by Neff and colleagues [9].

By March 1946, Gray and Halton [10] had accumulated a massive and unrivalled experience with tubocurarine, of more than 1000 major cases, having started using it early in 1945 and rapidly adopting it as routine. They were, almost certainly, the first to use the pure alkaloid in anaesthesia. Theirs was not, however, the first paper on neuromuscular blockers from the U.K.: Mallinson had described the use of Intocostrin in a small series of patients in 1945 [11].

A wide variety of anaesthetics was used by Gray and Halton: intermittent thiopentone, nitrous oxide, cyclopropane, ether. A tracheal tube was not usually passed. Controlled ventilation was not used, but its virtues clearly recognized and a warning given about the danger of giving neuromuscular blocking drugs if the anaesthetist had not mastered this technique. Their paper "A Milestone in Anaesthesia? (d-Tubocurarine Chloride)" [10] described this experience, and came down with enthusiasm for the new agent: it is a paper of truly remarkable quality.

The salient ideas behind the Liverpool Technique developed over the years 1946–1952, the former date being marked by the "Milestone" paper and the latter by Gray and Rees' "The role of apnoea in anaesthesia for major surgery" [12]. The views, especially of Knight [6] and of Waters [7], had been especially influential right from the start. No ingredient was new, but the recipe was clear, logical and incisive, and was taught and promulgated with great energy and enthusiasm.

The anaesthetist, it was held, should use specific drugs for specific purposes—for the "triad" of anaesthesia, that is narcosis, "analgesia" and muscular relaxation originally suggested, in primitive form, in 1950 [13]. "Narcosis" was taken to imply complete loss of consciousness; the subtlety of unconscious memory had not, at that time, emerged, but was clearly thought about [14]. "Analgesia" was later realized to be a misnomer. If a patient is fully unconscious he or she can feel no pain; what was really implied was "reflex suppression", that is the obtunding of such responses as bradycardia and hypotension, which can occur in a patient even when anaesthetized. The traditional "signs of anaesthesia", as many realized, were no longer applicable [15].

Both narcosis and reflex suppression, it was held, could be subserved by nitrous oxide (50 % in oxygen originally; later increased to 70 %), unsupplemented by volatile agents, which were virtually discontinued. If autonomic reflexes were troublesome during surgery other drugs, such as atropine, should be used; the analgesics were generally not very effective.

By 1952 and, indeed, before that date, it was realized that pulmonary ventilation should always be controlled [12]. Assisted ventilation was inefficient and full control, it was held, reduced the amount of other drugs needed [16]. The "tetrad" was complete: narcosis, reflex suppression, muscular relaxation and "controlled apnoea".

There were other important features of the technique. Tracheal intubation had long since come to be considered mandatory; it should be performed under tubocurarine; neuromuscular blockers should not be mixed and, if suxamethonium was indicated, the dose of tubocurarine should be reduced. The initial dose of tubocararine used had become greater, 40 mg being usual for long operations, with a preliminary 5 mg as a test dose before an induction, which was with thiopentone or, in poor risk cases, nitrous oxide and oxygen only. It was particularly important that neostigmine be administered routinely, to counteract residual block, in doses of 5 mg, mixed with, or preceded by, atropine 1.2 mg. Neostigmine was probably in use in the U.S.A. early on and Mallinson had had it to hand, but did not have to use it. Prescott, Organe and Rowbotham [17] had advocated its occasional use in 1946, in doses of 5 mg or more. Their use of large doses was clearly influential in Liverpool. The use of neostigmine in this way remained controversial. The patient should be awake within a few minutes and essentially able to look after himself or herself. Pain should be treated immediately with opioids before the patient was sent back to the ward. The problem of nursing postoperative patients who were deeply unconscious was avoided and the incidence of vomiting, the curse of ether days, was very substantially reduced.

The ideas behind the tetrad permeated all branches of anaesthesia, but of special importance was the contribution made by Rees, in introducing this system into paediatric anaesthesia. This development had a great and reforming influence locally, nationally and internationally.

A note should be added about a later development, the use of passive pulmonary hyperventilation. Most anaesthetists would accept that rhythmic ventilation of the lungs somehow contributes to quiescence during light anaesthesia when a neuromuscular blocker is used. Why this should be is not so clear. This led the Liverpool School to use this technique and to regard it as a flexible adjunct to anaesthesia [18], and stimulated an inconclusive debate about the possibility of cerebral hypoxia when this technique was used. Older soda-lime canisters were probably inefficient: because of the advent of larger canisters, massive hyperventilation resulted in profound hypocapnia. This was not proved to be dangerous, but was deemed to be unnecessary and a device became commonly used to limit hypocapnia whilst preserving advantages of rhythmic hyperventilation [19]. This became redundant when it became possible to use volatile agents, in metered, low doses. It still was customary to aim for hypocapnia, but only of modest degree.

Criticisms

For a long time many regarded relaxant anaesthesia as fundamentally unsafe. The best demonstration of this view was provided, in 1954, by Beecher and Todd in the U.S.A. [3] in their large survey of deaths related to anaesthesia. Their salient message was that there was good reason to suppose that anaesthesia with curare was very dangerous. Their conclusions were, on the whole, cautious, but not quite cautious enough. In particular, their conclusion that curare might have inherent toxicity, including cardiovascular toxicity, was ill-founded. In retrospect, it can be seen that they were demonstrating the need for a radically new approach to the use of these new agents, such as the Liverpool School was providing. Curare was not causing deaths; inappropriate techique was.

The term "neostigime-resistant curarization" was coined by Hunter in 1956 [20]. He described a group of "elderly and dilapidated patients", mainly with intestinal obstruction, who were given non-depolarizing neuromuscular blocking drugs and who subsequently showed an apparent failure in the antagonism of block with neostigimine. Neuromuscular transmission was not adequately tested. The problem was a genuine one, but its aetiology was probably multiple.

A later criticism of the Liverpool Technique was that patients were frequently aware, or only half asleep. The virtues of nitrous oxide as the sole agent were certainly overstated, but when the original technique is applied meticulously, the incidence of true awareness with subsequent recall is small and that of recall with unpleasant consequences smaller still, although unpleasant dreams are a problem [21]. Faulty techique can be disastrous in this respect, and this remains true today of anaesthesia with neuromuscular blocking drugs, even when supplementation is apparently generous.

The impact of new drugs and new equipment

Halothane made its clinical debut in 1956 and the use of controlled ventilation for operations not involving muscular relaxation started to decline. When vaporizers became available and small concentrations could be used reliably as a supplement, while preserving the virtues of light anaesthesia, its use became popular. It has now, of course, been largely superseded by other agents, but the principle of using them in small concentrations remains.

The newer analgesic agents, phenoperidine and fentanyl, were, in contrast, appreciated rapidly. Here were powerful reflex suppresssants which need not interfere with rapid recovery or cause hypotension, and they were incorporated into the technique. Tubocurarine was still in use until recently, although many had abandoned it for pancuronium or alcuronium. The newer agents, particularly atracurium, were greeted with enthusiasm.

Although agents have been changed and the emphasis shifted by recent advances, the principles behind the "tetrad" approach light anaesthesia with neuromuscular blocking drugs and controlled ventilation, remain. This has made a great contribution to safe anaesthesia.

J. E. Utting
Liverpool

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ORIGINAL ARTICLES

HYPOXAEMIA AND PAIN RELIEF AFTER LOWER ABDOMINAL SURGERY: COMPARISON OF EXTRADURAL AND PATIENT-CONTROLLED ANALGESIA

T. H. MADEJ, R. G. WHEATLEY, I. J. B. JACKSON AND D. HUNTER

SUMMARY

We have examined postoperative pain in patients allocated randomly to receive extradural bolus diamorphine 3.6 mg, extradural infusion of 0.15% bupivacaine with 0.01% diamorphine or patient-controlled i.v. administration of diamorphine at a maximum rate of 1 mg per 5 min, after total abdominal hysterectomy. Extradural infusion analgesia produced the smallest pain scores from 12 to 24 h after surgery ($P < 0.05$). More patients in the extradural infusion group were moderately hypoxaemic ($Sp_{O_2} < 90\% > 12$ min h^{-1}) after operation, compared with the two other groups ($P < 0.05$). The group using patient-controlled analgesia received more diamorphine and suffered a greater incidence of emetic sequelae ($P < 0.05$). (Br. J. Anaesth. 1992; **69**: 554–557)

KEY WORDS

Analgesia: extradural, patient-controlled. Complications: hypoxaemia. Pain: postoperative.

A recent report highlighted the inadequacy of pain relief after operation [1]. I.m. opioids given on an "as required" basis result in poor pain relief in up to 80% of patients [2], but newer techniques such as extradural opioids and patient-controlled analgesia may offer some advantages.

Ventilatory depression is a potentially life-threatening complication of any type of opioid analgesia. Pulse oximetry combined with computerized storage and analysis of data provides a method of continuously monitoring Sp_{O_2} at the patient's bed side [3].

In a previous study comparing i.m., patient-controlled and extradural opioid analgesia, bolus extradural diamorphine was found to produce mild postoperative hypoxaemia for longer periods than the two other methods [4]. Extradural infusion of dilute local anaesthetic with opioid solutions is an alternative to bolus administration and has several potential advantages, including provision of a more constant level of analgesia, reduced opportunity for introducing infection and possibly a lesser incidence of respiratory depression by removing the bolus effect. In the present study, we have compared extradural bolus with extradural infusion and patient-controlled analgesia using a 5-min "lock-out".

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Written informed consent was obtained from 50 healthy patients undergoing total abdominal hysterectomy.

One hour before operation, patients received temazepam 30 mg orally. Anaesthesia was induced with propofol 2 mg kg^{-1}, followed by vecuronium 0.1 mg kg^{-1} and IPPV with nitrous oxide and enflurane in oxygen. After induction of anaesthesia, a lumbar extradural block was produced with 0.5% bupivacaine 15–20 ml. The patients were allocated randomly, using a table of random numbers, to receive extradural or patient-controlled analgesia after operation.

Twenty patients (group EB) received an extradural bolus of diamorphine 3.6 mg in 0.9% saline 9 ml administered by the anaesthetist or senior nursing staff when requested by the patient. This was repeated as required during the first 24 h. Ten of these patients had participated in a previous study [4]. Twenty patients (group EI) received an extradural infusion of 0.15% bupivacaine with 0.01% diamorphine 4–6 ml h^{-1}. Ten patients (group PCA5) self-administered i.v. diamorphine at a maximum rate of 1 mg every 5 min using a Graseby Patient Controlled Analgesia System. In each case, the total dose of diamorphine received in the first 24 h after operation was recorded.

Arterial oxygen saturation was monitored continuously during the preoperative night and for 24 h after operation, while the patient breathed air, using a Nellcor N-100 pulse oximeter interfaced with an Opus IBM-compatible microcomputer [3]. Recordings of Sp_{O_2} were made every 10 s and stored by the computer so that 360 samples were obtained every 1 h. The percentage time spent with Sp_{O_2} $< 94\%$ $\geqslant 90\%$, $< 90\%$ $\geqslant 85\%$ and $< 85\%$ was analysed for the three groups and individual patients. For each patient, we defined mild hypoxaemia as $Sp_{O_2} < 94\%$ for more than 20% of each epoch—that is 12 min h^{-1} [5]. Moderate hypoxaemia was defined as $Sp_{O_2} < 90\%$ for the same proportion of time and

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T. H. MADEJ, F.R.C.ANAES.; R. G. WHEATLEY, F.R.C.ANAES.; I. J. B. JACKSON, F.R.C.ANAES.; D. HUNTER, R.G.N.; Department of Anaesthesia, York District Hospital, Wigginton Road, York YO3 7HE. Accepted for Publication: June 24, 1992.

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TABLE I. *Patient details and diamorphine use (mean (range)).* ***$P < 0.001$ *compared with groups EB and EI*

	Group PCA5 ($n = 10$)	Group EB ($n = 20$)	Group EI ($n = 20$)
Age (yr)	40	43	44
	(26–51)	(29–52)	(31–70)
Wt:ht^2 index	26.5	25.0	27.0
(kg m^{-2})	(20–35)	(22–33)	(20–36)
Diamorphine	41***	14.5	10.5
(mg/24 h)	(26–75)	(7.2–18)	(7.5–20)

TABLE II. *Duration of hypoxaemia (min h^{-1}) (mean (95 % confidence interval)) before and after operation in the three treatment groups.* *$P < 0.05$ *compared with group EI*

	Group PCA5 ($n = 10$)	Group EB ($n = 20$)	Group EI ($n = 20$)
Before op.	0.67*	1.72*	8.82
< 94 %	(0.26–1.09)	(0–3.94)	(0–34.78)
After op.	11.00	10.14*	22.00
< 94 %	(4.40–17.62)	(4.86–15.42)	(12.70–31.31)
After op.	1.42	1.28	6.67
< 90 %	(0.10–2.73)	(0.19–2.36)	(1.37–11.98)

TABLE III. *Number of patients with hypoxaemia before and after operation.* *$P < 0.05$ *compared with other groups*

	Group PCA5 ($n = 10$)		Group EB ($n = 20$)		Group EI ($n = 20$)	
	Before	After	Before	After	Before	After
Mild	0	2	1	9	5	6
Moderate	0	0	0	0	0	5*

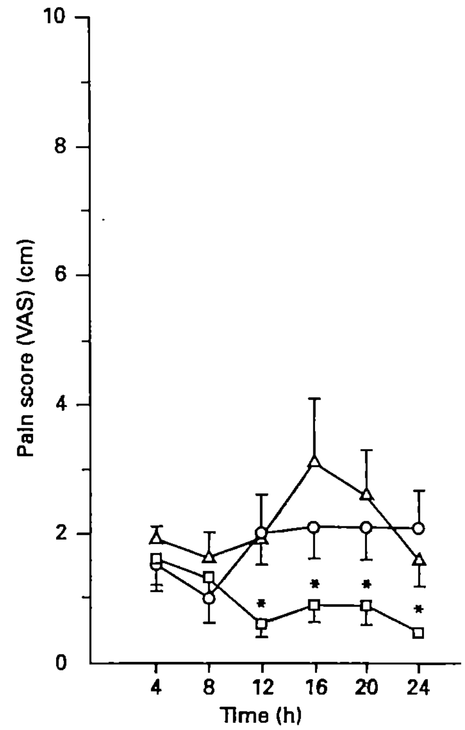

FIG. 1. Mean (SEM) visual analogue scale (VAS) pain scores 4–24 h after operation in groups PCA5 (△), EB (○) and EI (□). *$P < 0.05$ compared with groups EB and PCA5.

severe hypoxaemia as $Sp_{O_2} < 85\%$ for more than 10 % of each epoch or 6 min h^{-1}. The pattern of Sp_{O_2} was also represented graphically. Curves of Sp_{O_2} distribution *vs* percentage time for each hour were "stacked" to show the whole observation period, hour by hour, as a compressed array of curves. If the hourly mode Sp_{O_2} varied by more than 4 %, the array was considered to be unstable [4]. The number and duration of episodes of moderate ($Sp_{O_2} < 90\% > 20$ s) and severe ($Sp_{O_2} < 85\% > 20$ s) hypoxaemia were noted for each observation period.

Pain scores were obtained 4-hourly after operation using a 10-cm visual analogue scale. In addition, patients were asked to give an overall assessment of their postoperative analgesia at 24 h using a verbal rating score: poor, fair, adequate or excellent. A record was made of side effects including nausea, vomiting, pruritus and requirement for bladder catheterization.

Data were analysed using the Northwick Park Statistical package on an IBM-compatible computer (MS-DOS V3.2). Analysis of variance and Welch's test were used for parametric data. Fisher's exact test was used to analyse non-parametric data.

RESULTS

The three treatment groups did not differ in age or degree of obesity. There were a similar number of cigarette smokers in each group. Surgery and anaesthesia were uncomplicated in all 50 patients, with similar durations of operation and blood loss in the three groups. The amount of diamorphine used in the first 24 h by the patients in group PCA5 was significantly greater than that in the patients with extradural analgesia ($P < 0.001$) (table I).

Patients in group EI spent more time with $Sp_{O_2} < 94\%$ before operation compared with the two other groups ($P < 0.05$). After operation, group EI spent more time with $Sp_{O_2} < 94\%$ than did group EB ($P < 0.05$) (table II).

One patient in group EB and five in group EI were mildly hypoxaemic during preoperative monitoring of arterial oxygen saturation. After operation, nine of 20 EB, six of 20 EI and two of 10 PCA5 patients were mildly hypoxaemic. Five patients in group EI were moderately hypoxaemic after operation. Only one of these patients had been mildly hypoxaemic before operation; this patient was a non-obese, 51-yr-old smoker, who spent >30 % of the preoperative monitoring period with $Sp_{O_2} < 94\%$. After operation, she spent > 50 % of the time with $Sp_{O_2} < 94\%$, > 25 % of the time < 90 % and > 8 % of the time < 85 %. No patient in either of the other groups spent 20 % of the postoperative period with arterial oxygen saturations less than 90 % ($P < 0.05$). No patient experienced severe hypoxaemia (table III).

Analysis of episodes of moderate and severe hypoxaemia demonstrated that no patient spent more than 3 min with $Sp_{O_2} < 90\%$, or more than 1.5 min with $Sp_{O_2} < 85\%$ before operation. After operation, four patients in group EB spent periods of 7–90 min, seven patients in group EI spent 4–67 min and two patients in the PCA5 group spent 13–49 min with

TABLE IV. *Number of patients with side effects.* *P < 0.05 *compared with other groups*

	Group PCA5 ($n = 10$)	Group EB ($n = 20$)	Group EI ($n = 20$)
Emetic sequelae	9*	10	7
Sedation	7	8	13
Pruritus	1	8	5

$Sp_{O_2} < 90\%$. One patient in group EB spent up to 5 min, three in group EI spent 2–18 min and four in group PCA5 spent 2–3 min with $Sp_{O_2} < 85\%$.

At 24 h after surgery, 75 % of the extradural and 90 % of the PCA patients considered their postoperative analgesia to have been excellent. The majority of patients in all three groups were very comfortable, with mean pain scores of less than 4 cm (fig. 1). Patients with extradural infusions had smaller pain scores at 12–24 h after operation compared with the two other groups ($P < 0.05$).

The incidence of side effects is summarized in table IV. Emetic sequelae were common. In group PCA5, 90 % of patients experienced severe nausea or vomiting in the first 24 h after operation, but group EI had a lesser incidence of emetic sequelae ($P < 0.05$). The incidence and severity of sedation did not differ between the three groups. A similar number of patients in each group reported pruritus on enquiry at 24 h. No patient complained spontaneously or sought treatment for this side effect.

DISCUSSION

This study was a continuation of earlier work and was carried out in the Gynaecological unit with the same nurses and consultant surgeons. Ten of the patients in group EB had participated in an earlier study [4]. Their results are included for completeness and do not differ from the 10 more recently studied patients in group EB.

Patients in group EB spent a duration of time at $Sp_{O_2} < 94\%$ after operation similar to that in group PCA5. In the conditions of this study, they were as comfortable and as satisfied as group PCA5, despite a similar high incidence of emesis. In routine clinical practice, failures of extradural bolus opioid analgesia are difficult to deal with other than in an intensive care or high dependency area. We no longer provide an "as required" extradural bolus opioid service, because of early concerns about mild hypoxaemia, the problems of dealing with inadequate analgesia and a lack of adequately trained staff.

Interpretation of group oximetry data was difficult because of the unexpected finding of more mild hypoxaemia before operation in group EI than in the two other groups. Five of the 20 patients in group EI were mildly hypoxaemic before operation. These patients had an age range of 41–65 yr, weight:height indices of 21–31 kg m^{-2} and no other risk factors. The only means of identification was by analysis of the preoperative oximetry. If this had been done before randomization to groups, the groups could have been stratified for preoperative hypoxaemia. However, five patients in group EI were moderately hypoxaemic after operation, but only one had been mildly hypoxaemic before operation. Moderate hypoxaemia was not seen in the other two groups. Pain relief was excellent in group EI and this was most noticeable on the day after surgery when the patients started to mobilize. However, even with dilute infusions of local anaesthetic, the lumbar extradural restricted independent mobilization. One patient developed a deep venous thrombosis, another developed a pressure sore in legs lacking motor power, a third suffered weakness for several days after the extradural infusion was stopped and all patients were restricted further by routine urinary catheterization. We now limit extradural infusion analgesia after lower abdominal surgery to specific medical indications and complex surgery.

Group PCA5 demonstrated increased opioid use with increased availability. These patients, with a 5-min lockout, used 30 % more than those in an earlier study with a 20-min lockout [4]. However, this was still less than 12.5 % of the maximum available. A short lockout is required if a background is not provided, so that patients can load themselves and "catch up" as necessary. We do not use background infusions because of evidence of hypoxaemia and detrimental increase in use [6, 7]. The bolus dose was double that of morphine 1 mg currently recommended, diamorphine having been shown to have double the potency of morphine in this situation [8, 9]. Patients in group PCA5 had small pain scores, although not as good as those in patients in group EI, and they increased to a peak at 16 h after operation. These patients underwent surgery in the afternoon and they became increasingly active at 16 h after operation during the morning after surgery. The visual analogue scores were recorded in both rest and active states, but in the same state for all groups at each time. Group PCA5 had a greater incidence of emetic sequelae than group EI and also i.m. and PCA groups with a 20-min lockout. There are several possible explanations for this, including increased use of opioid, lack of routine prophylactic antiemetic medication and reluctance of nurses to administer and patients to request i.m. antiemetic medication [10]. Patients were very satisfied with this method of analgesia (despite the emesis) because of good pain relief, availability and control.

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HYPOXAEMIA AND PAIN RELIEF AFTER UPPER ABDOMINAL SURGERY: COMPARISON OF I.M. AND PATIENT-CONTROLLED ANALGESIA

R. G. WHEATLEY, D. SHEPHERD, I. J. B. JACKSON, T. H. MADEJ AND D. HUNTER

SUMMARY

Forty patients recovering from upper abdominal surgery were allocated randomly to receive i.m. morphine 0.15 mg kg^{-1} as required or patient-controlled analgesia (PCA), with i.v. morphine 1 mg and a 5-min lock out time. Arterial oxygen saturation (Sp_{O_2}) was measured continuously the night before and for 24 h immediately after surgery. A significantly greater proportion of patients in the PCA group (nine of 19) rated their analgesia as excellent compared with the i.m. group (two of 20) ($P < 0.05$). There was no significant difference in the incidence of postoperative hypoxaemia in the two treatment groups. Severe postoperative hypoxaemia ($Sp_{O_2} < 85\%$ for more than 6 min h^{-1}) was seen in three patients receiving i.m. analgesia and one patient in the PCA group. (Br. J. Anaesth. 1992; **69**: 558–561)

KEY WORDS

Analgesia: patient-controlled, intramuscular. Complications: hypoxaemia. Pain: postoperative.

A major factor limiting the use of patient-controlled analgesia (PCA) is the fear of respiratory depression. In a recent survey of postoperative analgesic practice in Anaesthetic departments in England and Wales, PCA was felt by 58% of respondents to be the ideal method of analgesia where there were no limitations in staffing or equipment [1]. However, only 18% rated it as the safest technique on normally staffed wards. In contrast, 63% of departments felt that on-demand i.m. analgesia was the safest form of analgesia. These fears about the safety of PCA are based on isolated reports of equipment failure [2] and the potential of the patient to administer an overdose of i.v. opioid drug. The aim of this study was to compare the efficacy and respiratory effects of PCA and i.m. analgesia after elective upper abdominal surgery using a bedside, computerized system of analysis and display of continuous Sp_{O_2} monitoring described previously [3].

PATIENTS AND METHODS

We studied 40 patients (aged 20–80 yr; ASA I or II) undergoing elective upper abdominal surgery. All gave written, informed consent to the study, which was approved by the Hospital Ethics Committee.

The patients were anaesthetized after oral temazepam premedication, with a standardized general anaesthetic technique comprising propofol 2 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} and nitrous oxide and enflurane in oxygen. Intraoperative analgesia was provided with fentanyl 2–4 µg kg^{-1}. Both groups of patients were made comfortable in the recovery room, when necessary, by administration of i.v. morphine. The patients were then allocated randomly to receive either i.m. analgesia or PCA after operation.

In the i.m. group, 20 patients received morphine 0.15 mg kg^{-1} i.m. 4-hourly on request. In the PCA group, 20 patients self-administered i.v. morphine at a maximum rate of 1 mg every 5 min using a Graseby Patient Controlled Analgesia system (PCAS). All patients were able to use the device within 1 h of the end of surgery.

The total dose of morphine administered to each patient in the first 24 h was noted.

Pulse oximetry

Continuous monitoring of arterial oxygen saturation (Sp_{O_2}) was peformed on the night before surgery and for the first 24 h after operation whilst the patient breathed air. The Sp_{O_2} monitoring was carried out using a Nellcor N-100 pulse oximeter interfaced with an Opus IBM-compatible microcomputer.

Recordings of Sp_{O_2} were made every 10 s and stored on the computer. The data were analysed by the computer and displayed in three ways:

(1) *Percentage and distribution of recorded Sp_{O_2}.* The values recorded during the whole observation period were displayed as min h^{-1} within a range of SpO_2 values: $< 85\%$; $\geqslant 85 < 90\%$; $\geqslant 90 < 94\%$; $\geqslant 94\%$.

Grades of hypoxaemia were defined as: mild = $Sp_{O_2} < 94\%$ for more than 12 min h^{-1} [4]; moderate = $Sp_{O_2} < 90\%$ for more than 12 min h^{-1}; severe = $Sp_{O_2} < 85\%$ for more than 6 min h^{-1}.

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TABLE I. *Patient data (mean (range))*

	I.m. group ($n = 20$)	PCA group ($n = 19$)
Age (yr)	50 (21–71)	53 (24–79)
Wt: ht^2 ($kg\ m^{-2}$)	25.2 (17–38)	25.3 (19–37)
Morphine (mg/24 h)	54 (22–100)	51 (17–90)
Blood loss (ml)	195 (138–251)	153 (61–241)
Duration (min)	63 (55–72)	61 (46–77)

TABLE II. *Duration of hypoxaemia (min h^{-1}) (mean (95% confidence limits)) before and after operation in the two treatment groups*

	PCA group ($n = 19$)	I.m. group ($n = 20$)
Before op.		
< 94%	7.7 (1.3–14)	12.5 (4.2–20.8)
After op.		
< 94%	18.0 (7.6–28.3)	25.7 (15.4–36.0)
< 90%	4.2 (1.0–7.3)	8.4 (2.8–13.9)
< 85%	0.5 (0–1.3)	1.9 (0–4.0)

TABLE III. *Number of patients with hypoxaemia before and after operation*

	PCA group ($n = 19$)	I.m. group ($n = 20$)
Before op.		
Mild	3	6
After op.		
Mild	2	3
Moderate	5	6
Severe	1	3

TABLE V. *Comparison of pain scores and morphine doses (mean (SD) in hypoxaemic and non-hypoxaemic i.m. patients*

	No. patients	VAS pain score in 24 h	Morphine (mg/24 h)
Non-hypoxaemic	17	30 (16)	49.4 (17.1)
Hypoxaemic	3	62 (15.1)	81.6 (20.2)
P		< 0.01	< 0.01

(2) *Graphic representation of the pattern of Sp_{O_2} distribution.* The computer was programmed to produce a curve of Sp_{O_2} distribution *vs* percentage of each hour. An array of curves was produced, "stacked" to show the whole observation period hour by hour as a compressed array of curves.

(3) *Hypoxaemic episodes.* The number and duration of episodes of severe hypoxaemia (Sp_{O_2} < 85% for longer than 20 s) were noted during each observation period.

Postoperative assessment

Pain scores were obtained 4-hourly using a 10-cm visual analogue scale (VAS). In addition, patients were asked to rate their postoperative pain relief using a verbal rating score: poor, fair, adequate and excellent.

Statistical analysis

Data were analysed using the Northwick Park statistics package on an IBM-compatible computer (MS-DOS 3.2). Unpaired *t* tests and Welch's test were used for parametric data. Non-parametric data was analysed using chi-square with Yates' correction.

RESULTS

The two treatment groups did not differ in age, sex distribution, degree of obesity or total dose of morphine used (table I). Surgery and anaesthesia were uncomplicated, with similar duration of surgery and blood loss in the two groups (table I). Operations performed were cholecystectomy (35), vagotomy and pyloroplasty (three) and anti-reflux operations (two).

Seventeen i.m. patients and 16 PCA patients were monitored on the night before surgery from approximately 22:00 to 07:00. The six patients with incomplete monitoring before operation had normal postoperative results and it is assumed that preoperative monitoring would not have revealed any major degree of hypoxaemia.

Six of the i.m. group and three of the PCA group were mildly hypoxaemic during the preoperative monitoring period. Severe hypoxaemia (Sp_{O_2} < 85% for more than 6 min h^{-1}) was not seen in any patient before operation, but one patient in each group had transient episodes of desaturation to less than 85% before surgery.

One patient in the PCA group had insufficient data collected for technical reasons and was excluded from the study. The remaining 39 patients were monitored for 20–24 h immediately after surgery.

There were no significant differences between the two groups in the duration of hypoxaemia either before or after operation (table II). However, it is interesting to note that the i.m. group spent a mean of 25.7 (SD 4.9) min h^{-1} with Sp_{O_2} less than 94%—an increase compared with preoperative mean values of 12.5 (3.9) min h^{-1} which just reached statistical significance ($P = 0.042$).

Table III shows the number of patients in each treatment group with mild, moderate or severe hypoxaemia. Severe hypoxaemia was seen in three i.m. patients and one patient receiving PCA. The preoperative status, age, degree of obesity, 24-h pain scores and dose of morphine used in these severely hypoxaemic patients are shown in table IV. The three i.m. patients with severe hypoxaemia had no

TABLE IV. *Data of patients with severe hypoxaemia (Sp_{O_2} < 85% for more than 6 min h^{-1})*

Group	Before < 94% (min h^{-1})	Age (yr)	Wt:ht^2 ($kg\ m^{-2}$)	VAS pain score in 24 h	Morphine (mg/24 h)
I.m.	1.2	36	28	69	85
I.m.	6	23	26	73	100
I.m.	3.6	67	24	45	60
PCA	11.4	51	37	66	65

TABLE VI. *Episodes of severe hypoxaemia*

Group	After op. < 85 % (min h^{-1})	No. episodes < 85 % > 1 min	Maximum duration (min)
I.m.	13.8	52	54.8
I.m.	11.4	232	7.6
I.m.	12	129	35.8
PCA	6.6	29	71.5

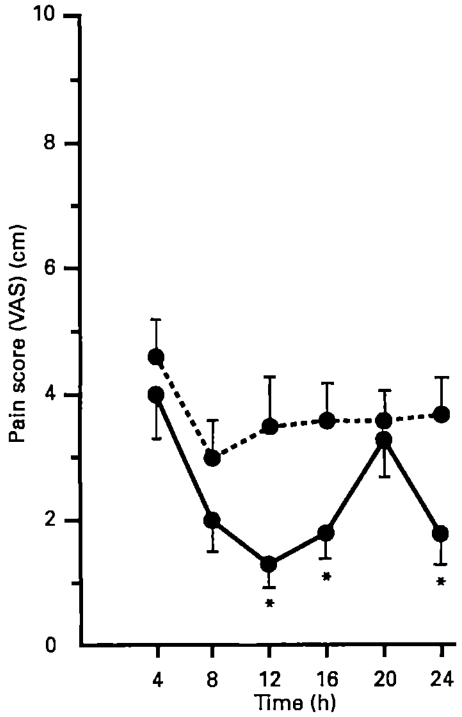

FIG. 1. Mean (SEM) VAS pain scores in the two treatment groups 4–24 h after operation. --- = I.m. group; —— = PCA group. * $P < 0.05$ compared with i.m.

evidence of preoperative hypoxaemia and were not significantly older or more obese than the non-hypoxaemic i.m. patients. They did, however, have significantly greater pain scores at 24 h and required larger doses of morphine ($P < 0.01$) (table V). The PCA patient with severe hypoxaemia was obese.

The number of episodes of severe hypoxaemia ($Sp_{O_2} < 85\,\%$ for longer than 20 s) and duration of the longest episode in the four patients with severe hypoxaemia are shown in table VI.

Patients receiving PCA had significantly lower VAS pain scores than the i.m. group at 12, 16 and 24 h ($P < 0.05$)) (fig. 1). In addition, a significantly greater proportion of patients in the PCA group (48 %) rated their analgesia as excellent compared with the i.m. group (10 %) ($P < 0.05$).

DISCUSSION

The intermittent i.m. adminstration of opioid drugs remains the mainstay of postoperative pain relief, being used routinely by 87 % of anaesthetic departments sampled in a recent survey [1]. Despite numerous reports of the inadequacy of this technique after major surgery, it continues to be used because it is felt to be the safest form of analgesia on normally staffed surgical wards.

In this study, PCA was associated with significantly better pain control, measured by VAS pain scores and patient satisfaction, than i.m. analgesia, without any evidence of increased hypoxaemia. In an earlier study [5] we defined mild hypoxaemia as occurring when the patient spent more than 6 min h^{-1} with an Sp_{O_2} less than 94 %. This was based on observations the night before minor surgery in young, healthy patients who spent 0.6 min h^{-1} with an Sp_{O_2} less than 94 %. Increasing experience of studying older patients undergoing more major surgery suggests that it is not uncommon for patients in this category to spend more than 6 min h^{-1} with an Sp_{O_2} less than 94 % in the preoperative period. We have therefore adopted the finding of Entwistle and colleagues [4] that more than 12 min h^{-1} with an Sp_{O_2} less than 94 % is a better indicator of significant hypoxaemia.

Despite numerous studies, it is still unclear what level of hypoxaemia is severe and what duration is critical and likely to cause harm in the postoperative period. Reeder and his colleagues [6] have shown that ST segment changes on Holter monitoring in patients recovering from abdominal vascular surgery are maximal on the third day and occur in those patients who have had desaturations to less than 85 %. For this reason, we have defined severe hypoxaemia as Sp_{O_2} less than 85 % for more than 6 min h^{-1} during the observation period and, in addition, we have determined the number and maximum duration of continuous episodes of Sp_{O_2} less than 85 %.

In previous studies [7] we have examined the effect of different forms of analgesia on the pattern of hypoxaemia in patients recovering from lower abdominal surgery. I.m. analgesia in this group of patients was associated with a low incidence of hypoxaemia. Severe hypoxaemia was rare, but moderate hypoxaemia occurred most commonly in those patients receiving excellent pain relief with extradural infusion analgesia. However, in upper abdominal surgery the degree of pain and the respiratory consequences of poorly relieved pain are more marked and effective pain control is more difficult to achieve.

The four patients with severe hypoxaemia in this study were all characterized by poor pain relief. The obese patient receiving PCA had poor pain relief despite self-administering morphine 65 mg in the first 24 h. The three i.m. patients with severe hypoxaemia had poor pain control with significantly greater pain scores, despite receiving significantly larger doses of morphine than the non-hypoxaemic i.m. patients. The limitations of i.m. analgesia are attributed usually to the patients receiving inadequate doses of analgesia. In this study, patients received frequent i.m. dosing, but had ineffective pain control and subsequently became hypoxaemic.

Preoperative nocturnal Sp_{O_2} values have been recommended as predictor of postoperative hypoxaemia [4, 5]. In this study, the three severely hypoxaemic i.m. patients had no evidence of preoperative hypoxaemia, even when studied overnight.

The results of this study on the role of analgesia in the development of postoperative hypoxaemia would suggest that PCA is not associated with an increased risk of severe hypoxaemia compared with i.m. analgesia, and that severe hypoxaemia can occur in upper abdominal surgery in patients with poor pain relief.

In view of the clinical significance of persistent postoperative hypoxaemia in the development of myocardial ischaemia [6], and the experimental evidence about the role of oxygen lack in cerebral dysfunction [8], wound healing [9] and infections [10], further investigation is required into the use of pulse oximetry in the prediction and detection of severe hypoxaemia, the value and duration of supplementary oxygen therapy and the use of balanced analgesia and opioid sparing analgesic techniques.

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British Journal of Anaesthesia 1992; **69**: 562–566

EFFECTS OF ISOFLURANE ANAESTHESIA ON THE MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIAL IN CHILDREN†

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SUMMARY

Evoked potentials are used to determine the integrity of neural pathways during neurosurgical and orthopaedic procedures, but the extent to which they may be altered by anaesthetic agents has not been studied systematically in children. In this study we have recorded median nerve somatosensory evoked potentials (mnSSEP) in children during isoflurane anaesthesia to determine if there are changes similar to those seen in adults. We studied 10 patients using standardized anaesthetic and clinical neurophysiological techniques. Control mnSSEP were obtained with 70% nitrous oxide in oxygen and isoflurane was then administered at 0.25, 0.50 and 0.75 MAC. The latencies and amplitudes of the mnSSEP were subjected to repeated measures analysis of the variance (ANOVA) and linear regression. There were statistically significant increases in N20, P22 latencies and central conduction time ($P < 0.001$) and reductions in amplitude of the N20-P22 complex ($P < 0.03$) with increasing end-tidal isoflurane concentrations. These results are similar to the findings in adults. (Br. J. Anaesth. 1992; **69**: 562–566)

KEY WORDS

Anaesthesia: paediatric. Anaesthetics, volatile: isoflurane. Brain: evoked potential. Nerve: median nerve.

Evoked potentials have been extensively investigated during anaesthesia [1]. Graded changes in latencies and amplitudes of the early cortical components of the somatosensory, auditory and visual evoked potentials occur with increasing end-tidal concentrations of inhalation agents in adults [2–6]. These have been proposed as an objective measurement of depth of anaesthesia in the prevention of awareness [7, 8].

Although evoked potential techniques are now used increasingly in anaesthetized children to determine the integrity of neural pathways during neurosurgical and orthopaedic procedures, no substantive study has been performed of the associated effects of anaesthesia on the evoked potentials in children. Measurement of evoked potentials in children is technically more difficult than in adults, and in commencing this investigation of the effect of these agents in young children the median nerve somatosensory evoked potential (mnSSEP) was chosen. This produces a robust, large-amplitude response which seemed more suitable for this study than middle latency auditory evoked potentials, which have been used in adult work, but which are inconsistently recordable in young children [9, 10]. The aim of our study was to determine the effects of isoflurane in nitrous oxide and oxygen on the latencies and amplitudes of the mnSSEP in children.

PATIENTS AND METHODS

After Ethics Committee approval, informed consent was obtained from the parents or guardians of 10 children aged between 10 months and 6 yr (mean 3 yr) presenting for surgery for repair of hypospadias. All patients were ASA I, with no known neurological deficit. All patients received a standard anaesthetic which was administered by a person who was not a project team member.

The children were premedicated 90 min before surgery with trimeprazine 4 mg kg^{-1} and atropine 0.04 mg kg^{-1} orally (this investigation was undertaken before the maximum recommended dose of trimeprazine was reduced to 2 mg kg^{-1}). Anaesthesia was induced with 3% halothane and nitrous oxide in oxygen and oral tracheal intubation was performed after i.v. administration of atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with 70% nitrous oxide in oxygen and caudal extradural anaesthesia with 0.25% bupivacaine 0.5 ml kg^{-1}. Positive pressure ventilation was used with a Siemens 900B ventilator at 12 b.p.m. to achieve an end-tidal carbon dioxide concentration of 5%. ECG, Sp_{O_2}, FI_{O_2}, FI_{N_2O} and nasopharyngeal temperature were recorded. End-

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TABLE I. *Recording techniques for mnSSEP in children*

Stimulation variables	
Site	Right median nerve at wrist
Electrodes	Percutaneous disc electrodes
Type	Direct current
Intensity	75 "volts"
Duration	0.2 ms
Inter-stimulus interval	270 ms
Recording variables	
Equipment	Digitimer D200
Sensitivity	100 $\mu V\ V^{-1}$
Band width	30 ms (time constant) to 3 Khz
Repetitions per run	275
Pre-stimulus analysis window	20 ms
Post-stimulus analysis window	55 ms
Scalp electrode type	Silver–silver chloride
Electrode impedance	< 3000 Ω
Electrode placement	Collodion fixation and electrode conduction gel
Recording montage	
Channel	Electrode derivations
1	Reference: frontal Active: cervical
2	Reference: frontal Active: left parietal
3	Reference: ipsilateral ear Active: left parietal

tidal concentrations of carbon dioxide and isoflurane were measured using a Datex Capnomac. The mean arterial pressure was recorded non-invasively every 3 min using a Dinamap 1846 Vital Signs Monitor. These data were then recorded onto magnetic tape and a paper recorder.

The mnSSEP were measured using a standard technique with a Digitimer D200 (Digitimer Ltd, Welwyn Garden City, Hertfordshire, England) (table I). All data were stored on a floppy magnetic disk and analysed off-line. The EEG signal from the active left parietal electrode referred to a right parietal electrode was recorded continuously onto magnetic tape and was processed by the Cerebral Function Analysing Monitor (CFAM). This arrangement allowed us to monitor both the EEG signal quality and the effects of anaesthesia. Evoked potential recordings contaminated by electrical interference from diathermy were rejected.

After non-stimulus controls, the measurement of mnSSEP was commenced 20 min after induction of anaesthesia, thus ensuring that the halothane had cleared, as confirmed by vapour analysis using the Datex Capnomac. Evoked potentials were recorded every 90–180 s until completion of the study. Six control mnSSEP were recorded before the start of surgery and isoflurane was introduced in a stepwise fashion to reach end-tidal concentrations equivalent to 0.25, 0.50 and 0.75 MAC, corrected for each child's age, but without a correction for the presence of nitrous oxide [11]. The required end-tidal isoflurane concentration was achieved using over pressure and was held constant for 15 min at each concentration.

Analysis of the mnSSEP was conducted off-line. The latencies from the stimulus to the N13, N20 and P22 components of the mnSSEP were measured and the central conduction time (CCT) (N20–N13) was derived. The peak amplitude of N13 was measured from the pre-stimulus baseline, while the amplitude of the N20–P22 complex was measured peak-to-peak. When the electrical stability of the mnSSEP had been achieved at each end-tidal concentration, the mean amplitudes and latencies were derived

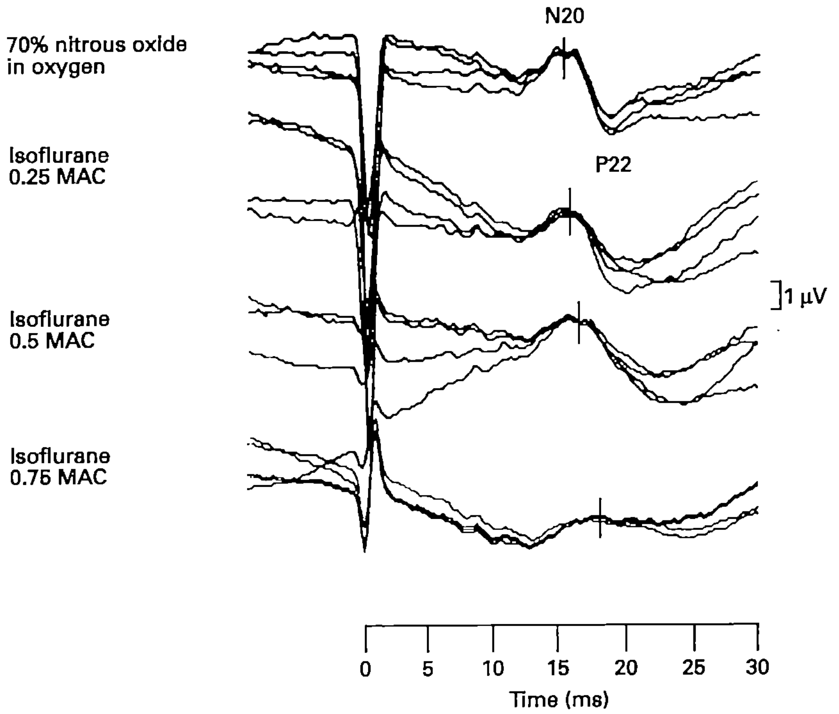

FIG. 1. Effects of isoflurane in 70 % nitrous oxide in oxygen on the mnSSEP of patient No. 3, showing increasing latency and reduction of amplitude of the N20–P22 complex with increasing concentrations of isoflurane. For each measurement, four consecutive evoked potentials are superimposed.

from four successive evoked potentials. Data were analysed using repeated measures analysis of the variance (ANOVA) and linear regression [12].

RESULTS

Satisfactory mnSSEP were recorded in all children; figure 1 illustrates the effect of isoflurane on the evoked potentials obtained from patient No. 3. The

TABLE II. *Effects of isoflurane in 70% nitrous oxide in oxygen on the mean* (SD) *latencies of the mnSSEP in 10 children.* ***$P < 0.001$

	Mean latency (ms)			
	N13	N20	CCT	P22
70% nitrous oxide in oxygen	7.49	15.64***	8.15***	22.14***
	(0.78)	(1.36)	(1.56)	(3.30)
0.25 MAC isoflurane	7.50	16.92***	9.42***	23.78***
	(0.78)	(1.74)	(1.88)	(3.49)
0.50 MAC isoflurane	7.50	18.23***	10.79***	26.20***
	(0.78)	(2.06)	(1.95)	(3.82)
0.75 MAC isoflurane	7.51	19.45***	12.04***	28.40***
	(0.77)	(2.56)	(2.40)	(3.58)

TABLE III. *Effects of isoflurane in 70% nitrous oxide in oxygen on the mean* (SD) *amplitudes of the mnSSEP in 10 children.* *$P < 0.03$

	Mean amplitude (μV)	
	N13	N20–P22 (Fz)
70% N_2O in O_2	3.85	3.34*
	(1.98)	(1.88)
0.25 MAC isoflurane	3.63	2.53*
	(2.10)	(1.33)
0.50 MAC isoflurane	3.93	2.08*
	(2.58)	(1.05)
0.75 MAC isoflurane	3.44	1.60*
	(2.03)	(0.88)

mean arterial pressure did not alter more than 15% in any patient. Nasopharyngeal temperatures were within 0.5 °C of control values in all patients.

In the presence of isoflurane there were significant differences in the grouped data between N13, N20 and P22 latencies and the CCT ($P < 0.001$, ANOVA) (table II). Comparing the slopes of latency against isoflurane concentration among the patients, there was no significant change in N13 latency with

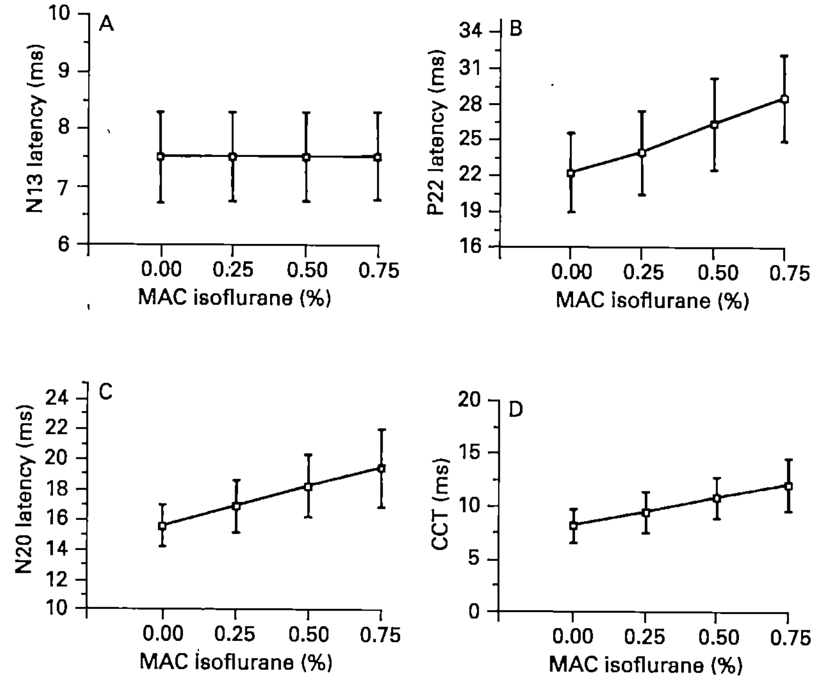

FIG. 2. Relationship between fractional MAC of isoflurane in 70% nitrous oxide in oxygen and mean (SD) N13 latency ($P > 0.05$) (A), P22 latency ($P < 0.001$) (B), N20 latency ($P < 0.001$) (C) and central conduction time (CCT) ($P < 0.001$) (D).

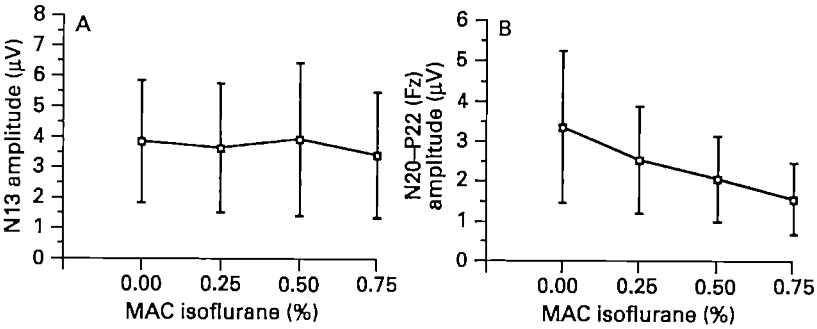

FIG. 3. Relationship between fractional MAC of isoflurane in 70% nitrous oxide in oxygen and mean (SD) N13 amplitude ($P > 0.05$) (A) and N20–P22 amplitude ($P < 0.05$) (B).

increasing concentrations of isoflurane. However, with N20, P22 and CCT there were significant increases in latency proportional to increasing concentrations of isoflurane ($P < 0.001$) (fig. 2).

There were significant differences in the response to isoflurane between N13 and N20–P22 amplitudes ($P < 0.05$, ANOVA) (table III, fig. 3). Comparing the slopes of amplitude against isoflurane concentration among the patients, there were no significant changes in the N13 amplitude with increasing concentrations of isoflurane. There were significant reductions in N20–P22 amplitude which were proportional to increasing concentrations of isoflurane ($P < 0.03$).

DISCUSSION

The aim of this study was to develop a technique for monitoring mnSSEP during anaesthesia in children, thus providing reference values for the effects of isoflurane on these potentials and enabling comparison with similar investigations in adults.

There are several factors not related to anaesthesia which may have influenced the results. The amplitude and latency of the mnSSEP are affected by age, body temperature, mean arterial pressure, end-tidal carbon dioxide concentration and surgical stimulation. The latencies of the mnSSEP in children are shorter than comparable potentials in adults, mainly because of differences in height. The expected N20 latency of children between the ages of 10 months and 6 yr is 15.7 (SD 0.94)–15.52 (0.54) ms [13]. The use of collective data in children with a wide age range may result in a large variance; although a large variance did occur, highly significant changes in latencies and amplitudes occurred at different fractional MAC of isoflurane. The changes in temperature and mean arterial pressure were not sufficient to affect the evoked potentials. Surgical stimulus is known to oppose the effect of inhalation agents on the latencies and amplitudes of the mnSSEP [14]; in this study, this effect was eliminated by the use of caudal extradural analgesia. This was confirmed by the absence of change in the cardiovascular variables in response to surgery or evoked potential recording and by the fact that all the patients had satisfactory analgesia at the end of the operation. In addition, observation of the CFAM traces showed no evidence of arousal responses during surgery [15].

Early investigations of evoked potentials during anaesthesia in animals and adult humans showed that increases in latency and reduction in amplitude of the cortical components occurred [16, 17]. More recent investigations have shown that these changes are graded to changes in end-tidal anaesthetic concentration [2–4, 18]. Most of the studies have involved a single inhalation anaesthetic agent; this investigation follows routine clinical anaesthesia in children using a balanced anaesthetic technique, including nitrous oxide in oxygen as background anaesthesia. Control measurements were taken after induction of anaesthesia in the presence of 70% nitrous oxide in oxygen; this may have reduced the absolute amplitude of mnSSEP, but probably had little effect on the latency [19]. As the end-tidal nitrous oxide concentration remained constant throughout the investigation, it seems reasonable to attribute any changes which occurred in the mnSSEP to different end-tidal concentrations of isoflurane.

This study has demonstrated in children, as in adults, that there were dose related changes in the N20 and P22 components of the mnSSEP with increasing end-tidal concentrations of isoflurane [2–4]. In addition, we have shown a differential effect of isoflurane on the central nervous system as the increase in CCT can be accounted for by the changing latency of the N20. Although changes in the amplitude of the N20–P22 complex were recognized easily on visual inspection of the traces, they were difficult to quantify. This may have been a result of several factors, but is most likely to be as a result of technical difficulties in defining a baseline reference point for measurement. These findings support the views of Samra and co-workers, who suggested that latency provided the better measure of anaesthetic effects on the mnSSEP [2].

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The authors thank Marion Hare (Department of Neurophysiology, Hospitals for Sick Children, Great Ormond Street, London) for her technical assistance and W. D. White, M.PH. and L. R. Smith, PH.D. (Duke University Medical Center, North Carolina) for their assistance with the statistical analysis.

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Gasproben in der Säuglingskapnometrie 307
Hypoxie in der unmittelbar postoperativen Phase 313
Neue Hydroxyethylstärke-Präparation 316
Zusatz von Äthylalkohol zur Spülflüssigkeit 324
Überwachung des Patienten im Aufwachraum 331
Propofol versus Midazolam 335
Beatmung neonatologischer Patienten 342
Entzündliche Fistel nach Periduralkatheter 346
Der Notruf 348
Postoperative Schmerztherapie nach Hyperekplexie 354
Knickung der Arteria carotis interna 361
Leserbriefe 365

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Histaminfreisetzung bei der Einleitung von Kombinationsnarkosen mit Nalbuphin oder Fentanyl *

Modulierung der Reaktion durch die Prämedikation Promethazin/Pethidin

W. Dick[1], W. Lorenz[2], D. Heintz[1], H. Sitter[2] und A. Doenicke[3]

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Zusammenfassung

In einer kontrollierten klinischen Studie an 24 allgemeinchirurgischen Patienten wurde die Histaminkonzentration während der Einleitungsphase einer Kombinationsnarkose mit Nalbuphin (1 mg/kg) oder Fentanyl (5 µg/kg) untersucht. Zur Prämedikation erhielten die Patienten Promethazin (Atosil®) und Pethidin (Dolantin®) 30 min vor den Opioiden. Die Narkoseeinleitung erfolgte mit Alcuronium-Flunitrazepam-Thiopental-Succinylcholin. Nach der Intubation wurde die Analgesie mit Nalbuphin oder Fentanyl aufrechterhalten. Nalbuphin und Fentanyl erwiesen sich als Histaminfreisetzer mit einer mehr als 40%igen Inzidenz; Nalbuphin aber modulierte (potenzierte) noch dazu die Histaminfreisetzung durch die Kombination Alcuronium-Flunitrazepam-Thiopental. Dieser Unterschied zwischen Nalbuphin und Fentanyl war statistisch signifikant (Inzidenz 46% gegen 9%!). Eine direkte Korrelation zwischen Histaminfreisetzung und hämodynamischer Instabilität konnte nicht nachgewiesen werden. Auch eine detaillierte Kausalitätsanalyse mit bedingten Wahrscheinlichkeiten und der Annahme einer beitragenden Determinante für Histamin ergab, daß die Histaminfreisetzung die gemessenen hämodynamischen Parameter kaum beeinträchtigt. Eine mögliche Ursache dieser Ergebnisse besteht in der zeitgerechten vorherigen Gabe von Promethazin, das sowohl eine starke H_1-antagonistische Wirkung wie auch eine H_2-antagonistische Wirkung entfaltet.

Schlüsselwörter

Histamin – Randomisierte Studie – Nalbuphin – Fentanyl – Antihistaminika

Histamine release during induction of anaesthesia with nalbuphine or fentanyl. Modulation of the reaction by premedication with promethazine/pethidine

Abstract

In a controlled clinical trial in patients admitted for general surgery (mainly abdominal and thyroid), histamine release following nalbuphine 1 mg/kg i.v. versus fentanyl 5 µg/kg i.v. was studied in the course of an otherwise routine induction with promethazine pethidine as premedication 30 min before the opioids and alcuronium - flunitrazepam - thiopental 5 min later. Succinylcholine was given before intubation and further analgesia was obtained by repeated administration of either nalbuphine or fentanyl. Plasma histamine levels were measured by a specific fluorometric assay, heart rate and blood pressure were measured for assessing hemodynamics and clinical signs of anaphylactoid reactions such as skin eruptions and arrhythmias were registered.

Results. Nalbuphine and fentanyl both released histamine with an incidence of more than 40%. In addition, nalbuphine potentiated the histamine release evoked by the sequential administration of alcuronium-flunitrazepam-thiopental in one complex of application. The incidence of histamine release in the nalbuphine group was 6/13 = 46%, in the fentanyl group only 1/11 = 9% (chi² test, $P < 0.05$). Furthermore this study showed high histamine levels after succinylcholine and intubation in a relation to time of administration that suggested histamine release as a stress response to intubation. Finally, the incidence of histamine release after a second injection of the opioids was still 30%. A direct correlation between plasma histamine levels, hemodynamic changes, and skin reactions could not be shown. A detailed causality analysis with histamine release as a contributory determinant showed histamine release less detrimental to hemodynamic stability than the opposite, which had been expected. However, the promethazine administered 30 min before induction of anaesthesia had strong H_1- and H_2-receptor antagonistic activity and was given with optimum timing for H_1- and H_2-prophylaxis.

Conclusion. The study demonstrated that histamine release during anaesthesia and surgery depends strongly on the time sequence of drugs and

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SEQUENTIAL MEASUREMENT OF THE MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIAL DURING ISOFLURANE ANAESTHESIA IN CHILDREN†

D. G. MASON, D. HIGGINS, S. G. BOYD AND A. R. LLOYD-THOMAS

SUMMARY

We have used sequential measurements of median nerve somatosensory evoked potentials (mnSSEP) in 10 children to estimate the equilibration time of an inhalation anaesthetic agent between alveolar gas, arterial blood and brain. MnSSEP were obtained sequentially every 90–180 s. After control measurements in the absence of isoflurane, the end-tidal concentration was increased stepwise (0.25, 0.5 and 0.75 MAC). Each isoflurane concentration was maintained for 15 min. The point at which the N20 latency reached stability was determined; the mean time between reaching a stable end-tidal isoflurane concentration and this point varied between 5 min 16 s and 7 min 37 s. This technique may be useful in circumstances in which a "steady state" of anaesthesia is important, such as in the determination of MAC or during intraoperative monitoring of evoked potentials. (Br. J. Anaesth. 1992; **69**: 567–569)

KEY WORDS

Anaesthesia: paediatric. Monitoring: median nerve somatosensory evoked potentials.

Graded changes in latency and amplitude of the median nerve somatosensory evoked potential (mnSSEP) with changing end-tidal concentrations of inhalation anaesthetic agents have been demonstrated in adults [1–3]. Similar graded changes occur in children with increasing concentrations of isoflurane [4]. In the investigation of this relationship, it is important to ensure that equilibration between alveolar gas, arterial blood and brain concentrations of the volatile agent has occurred before measuring evoked potentials (EP). This is to ensure that a steady state has been achieved before taking measurements. In the majority of such investigations in adults, a period of 10–15 min has been allowed between reaching the desired end-tidal concentration and measuring the EP [1, 2]. In the definition of the minimum alveolar concentration (MAC), 15 min should be allowed for this equilibration [5]. This equilibration period is determined mainly by the blood/brain partition coefficient of anaesthetic agents and known values of cerebral blood flow in adults. However, no technique has been devised which can determine this equilibration period for individual patients during administration of a volatile anaesthetic agent. Sequential mnSSEP measurements are used in this study, in an attempt to determine this equilibration period in children.

PATIENTS AND METHODS

We studied 10 children of ASA grade I without neurological deficit. Informed consent was given by their parents or guardians and the project was approved by the Ethics Committee of the Hospitals for Sick Children. A standard anaesthetic technique was used as described previously: in summary, this consisted of oral premedication with trimeprazine 4 mg kg^{-1} and atropine 0.04 mg kg^{-1} 90 min before induction of anaesthesia with 3% halothane in nitrous oxide and oxygen [4]. This was followed by atracurium 0.5 mg kg^{-1} to facilitate oral tracheal intubation. Maintenance of anaesthesia comprised 70% nitrous oxide in oxygen and caudal extradural anaesthesia using 0.25% bupivacaine 0.5 ml kg^{-1}. The lungs were ventilated using a Siemens 900B ventilator to produce an end-tidal carbon dioxide concentration of 5% at a rate of 12 b.p.m. Heart rate, ECG, Sp_{O_2}, FI_{O_2} and FI_{N_2O} and nasopharyngeal temperature were recorded together with the end-tidal concentration of carbon dioxide and isoflurane using a Datex Capnomac. Mean arterial pressure was recorded non-invasively every 3 min using a Dinamap 1846 Vital Signs Monitor. MnSSEP were measured as described previously [4]. After non-stimulus controls, EP were measured 20 min after the induction of anaesthesia, before introduction of isoflurane and at start of surgery. EP were recorded thereafter every 90–180 s in a sequential manner. The end-tidal concentration of isoflurane was noted

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David G. Mason*, m.b., b.s., f.r.c.anaes., David Higgins§, m.b., b.s., f.r.c.anaes., A. R. Lloyd-Thomas, m.b., b.s., f.r.c.anaes. (Department of Anaesthetics); S. G. Boyd, m.d. (Department of Clinical Neurophysiology); Hospitals for Sick Children, Great Ormond Street, London WC1N 3JR. Accepted for Publication: June 22, 1992.

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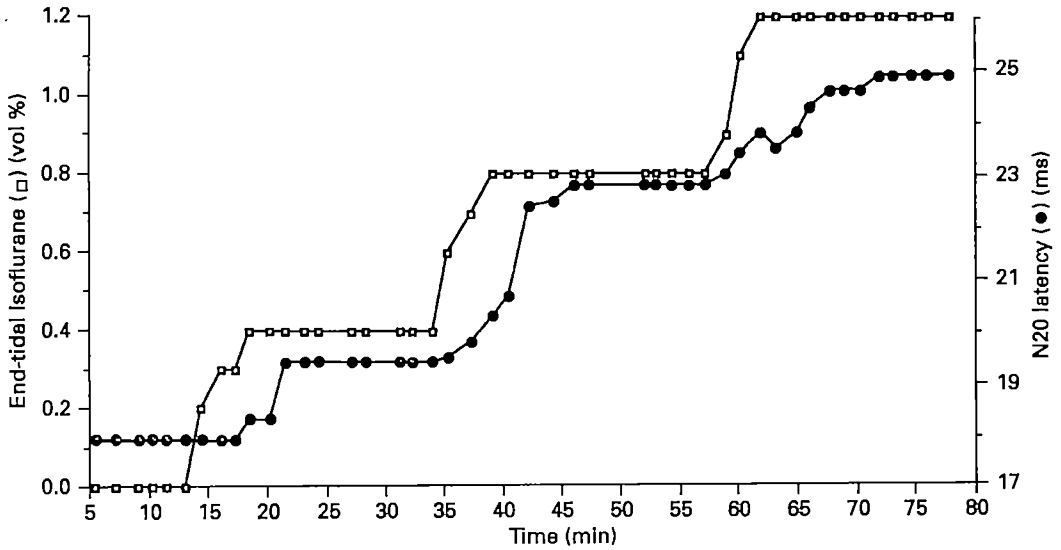

FIG. 1. Variations in N20 latencies (●) and end-tidal isoflurane (□) concentrations with time for patient No. 9.

at the end of each sequence. After six control EP in the presence of 70% nitrous oxide in oxygen, isoflurane was introduced stepwise to reach an end-tidal concentration equivalent to 0.25, 0.5 and 0.75 MAC (corrected for the age of each child, but not for the presence of nitrous oxide [5]). The required end-tidal concentrations of isoflurane were produced using over pressure and held constant for a 15-min period at each value. As in the previous investigation, EEG was recorded continuously [4]. All data were recorded onto magnetic disk and analysed off-line. The end-tidal isoflurane concentrations and N20 latencies for each child were plotted against time.

Data were analysed to determine the point of N20 latency stability by inspection, and confirmed using a technique of analysis of the ratio of the variance. For each MAC value, we used measurements of the ratio of the variance of successive groups of N20 latencies from end-tidal stability to the end of the 15-min period. The point at which the smallest ratio occurred was considered the point of N20 latency stability. The time from reaching a stable end-tidal isoflurane concentration to this point could then be determined at each MAC value and for each child.

RESULTS

Satisfactory mnSSEP were obtained from all children. Several sequences of EP contained electrical interference from diathermy and were not included in the data. It was not possible to obtain the time to N20 latency stability at 0.25 MAC isoflurane for patient No. 5 because of diathermy interference. The mean arterial pressure did not change by more than 15% of the control value in any patient and the nasopharyngeal temperature was within 0.5 °C of control values in all children.

The N20 latencies and the end-tidal isoflurane concentrations were plotted against time for each child. A curve and plateau was obtained at each MAC value for both the end-tidal isoflurane concentrations and N20 latencies. A delay between reaching a stable end-tidal MAC and achieving N20 latency stability was observed. Figure 1 shows such a plot for patient nine. The duration from reaching each stable fractional MAC of isoflurane to each stable N20 latency for each patient is shown in table I (related to age) and displayed graphically in figure 2.

TABLE I. *Time to N20 latency stability after achieving desired fractional isoflurane MAC in 70% nitrous oxide in oxygen*

Patient No.	Age (yr)	Time (s) 0.25 MAC	0.5 MAC	0.75 MAC
1	0.8	412	368	685
2	1	395	391	423
3	6	529	415	736
4	4	390	275	478
5	4.5		311	300
6	3	385	214	187
7	5	344	317	438
8	1.8	407	262	472
9	2.5	175	410	605
10	1	374	197	243
Mean	3	379	316	457
Range	0.8–6			
SD		91.96	78.99	181.74

DISCUSSION

Anaesthetic agents alter neurophysiological function and it seems reasonable to assume that there is a constant relationship between changes in evoked potential measurements and changes in concentration of anaesthetic agents in the brain [1]. The N20 latency is a convenient neurophysiological reference point for measuring the effects of anaesthetics on the brain in children, although it may not represent the primary site of action. With any inhalation anaesthetic agent, it takes a finite time for equilibration to occur between alveolar gas, arterial blood and the brain. The time taken for the N20 to stabilize after changes in end-tidal anaesthetic concentration is therefore likely to estimate this equilibration period.

The equilibration period is determined mainly by the solubility of the anaesthetic agent and the

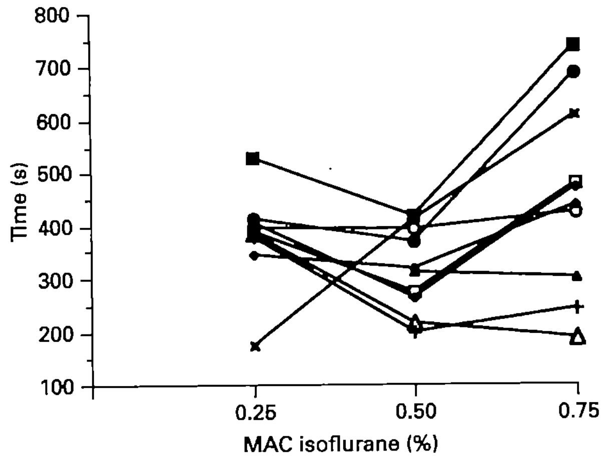

FIG. 2. Time to N20 latency stability after achieving each stable MAC isoflurane concentration. Each symbol represents results from a different patient; X = patient No. 9, for whom data were also presented in figure 1.

metabolic rate, which in turn is related to cardiac output and cerebral blood flow. In the determination of MAC, a 15-min period is allowed for this equilibration. This was derived from known values of cerebral blood flow and the blood brain coefficient of anaesthetic agents in adults. Quasha, Eger and Tinker noted that global cerebral blood flow values were used in the determination of this period [5]. However, anaesthetic agents have a major effect in specific regions of the brain which may have a greater blood flow, and therefore it is likely that 15 min is an overestimate of the equilibration period. In children, who have a greater metabolic rate than adults, one would expect equilibration to occur even more rapidly. In most of the patients investigated, the time to equilibration was less than 10 min, which would support this hypothesis.

Knowledge of the equilibration period between alveolar gas, arterial blood and brain of inhalation anaesthetics, and hence the effects of anaesthesia on neurophysiological function, has important practical applications. When investigating effects of anaesthesia on EP, it is essential that measurements are made during a steady state. One solution to this problem is to specify a fixed minimum interval between achieving a desired anaesthetic concentration and taking EP measurements. However, in previous studies, this interval has varied, which makes comparisons of the results less valid. For example, Samara and co-workers [1], Thornton and co-workers [6] and Nogueira and co-workers [7] allowed an equilibration period of 10 min, while Sebel and co-workers [2] allowed 15 min. Moreover, the present study showed considerable variation in the equilibration period, not only between individual children, but also between each fractional MAC of isoflurane; indeed, taking the whole group, the range was between 175 s and 736 s. If this same degree of variability is found in adults, a fixed period of 15 min may not be universally applicable. This would have implications for the determination of MAC of new volatile anaesthetic agents.

When using EP to monitor the integrity of neural pathways during surgery, it is important to be able to differentiate between changes caused by surgery and the effects of changes in anaesthesia and other non-surgical factors. More certain knowledge of the time taken to reach anaesthetic equilibration may therefore improve accuracy and confidence when EP changes are interpreted, particularly during critical periods of an operation.

The technique of sequential measurement of mnSSEP to determine the equilibration period described here could be applied to EP measurement in various situations in the operating theatre. Incorporating this technique into an on-line information system would enhance intraoperative EP monitoring and neurophysiological studies of the effects of anaesthetic agents.

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PROPOFOL AND ALFENTANIL IN CHILDREN: INFUSION TECHNIQUE AND DOSE REQUIREMENT FOR TOTAL I.V. ANAESTHESIA

B. L. BROWNE, C. PRYS-ROBERTS AND A. R. WOLF

SUMMARY

We estimated the dose of propofol (initial dose followed by a stepped infusion) when given with two different infusion rates of alfentanil for total i.v. anaesthesia in 59 children aged 3–12 yr. Patients in series 1 (four groups) received an alfentanil loading dose of 85 $\mu g\ kg^{-1}$ *and an infusion of 65* $\mu g\ kg^{-1}\ h^{-1}$*. Patients in series 2 (groups 5 and 6) received an alfentanil loading dose of 65* $\mu g\ kg^{-1}$ *and infusion of 50* $\mu g\ kg^{-1}\ h^{-1}$*. Parents gave their informed consent. Premedication comprised temazepam 0.3 mg* kg^{-1}*. Glycopyrronium 5* $\mu g\ kg^{-1}$ *was administered and anaesthesia induced and maintained with alfentanil (loading dose and infusion) followed by propofol (loading dose and three-stage manual infusion scheme). Suxamethonium 1 mg* kg^{-1} *was used to facilitate tracheal intubation and the lungs were ventilated artificially to normocapnia with 30% oxygen in air. Probit analysis was used to determine the dose requirement of propofol. In series 1, the* ED_{50} *was 6.0 mg* $kg^{-1}\ h^{-1}$ *(95% confidence limits 5.5–6.2 mg* $kg^{-1}\ h^{-1}$*) and* ED_{95} *8.6 (6.8–7.8) mg* $kg^{-1}\ h^{-1}$*. Corresponding values for series 2 were* ED_{50} *7.5 (8.0–9.8) mg* $kg^{-1}\ h^{-1}$ *and* ED_{95} *10.5 (9.6–13.1) mg* $kg^{-1}\ h^{-1}$*.* (Br. J. Anaesth. 1992; **69**: 570–576)

KEY WORDS

Anaesthesia: paediatric. Anaesthetic techniques: total intravenous anaesthesia. Anaesthetics, intravenous: propofol. Analgesics: alfentanil. Pharmacodynamics.

Propofol has become well established as an induction agent with excellent recovery characteristics [1–4]. In adults it has been used to induce and to maintain anaesthesia: alone, as a supplement to nitrous oxide, or in total i.v. anaesthesia with alfentanil or fentanyl [5–8]. In adults, the dose–response relationships have been established for infusion of propofol and alfentanil when used as the sole agents to maintain anaesthesia [9]. In children, propofol has been studied as an induction agent [10–12] and the dose has been established as 1.6–3 mg kg^{-1} [13, 14]. The aim of the present study was to determine the dose requirement of propofol when used with alfentanil as a total i.v. anaesthetic technique in children.

We used a three-stage manual infusion scheme for propofol designed to achieve and maintain a steady blood concentration of propofol [9, 15, 16]. As nitrous oxide was not used, alfentanil was chosen to provide analgesia to supplement the propofol infusion. Initial estimates of the likely infusion requirement were based on the pharmacokinetic studies of alfentanil available at the time [17–19], our aim being to achieve a plasma concentration similar to that which, in adults, provided satisfactory conditions for surgery [20, 21].

As prolonged alfentanil infusions could cause ventilatory depression during the postoperative period, the study was repeated at a slower infusion rate of alfentanil. The increased requirement for propofol was then determined in another 23 children.

PATIENTS AND METHODS

The study was approved by the District Ethics Committee. Informed consent was obtained from the parents of 59 otherwise healthy children presenting for body surface surgery (herniotomy, orchidopexy, closure of patent processus vaginalis, *etc.*). Most of the surgery was performed in boys, with only four girls selected. Each child was allocated sequentially to one of six groups (table I). Obese children (more than 20% greater than their expected weight for height), those who were not either ASA I or II, and any who had experienced a drug reaction during previous anaesthesia were excluded.

Children received temazepam 0.3 mg kg^{-1} 1–2 h before operation and "EMLA" (eutectic mixture of local anaesthetic, Astra Pharmaceuticals) was applied to the dorsum of both hands. Two 60-ml syringes and two calibrated Vickers IP4 infusion pumps were primed respectively with propofol 10 mg ml^{-1} and alfentanil 100 $\mu g\ ml^{-1}$. The alfentanil was diluted deliberately, in saline, so that reasonable infusion rates of administration could be used; alfentanil is stable for more than 24 h in saline [data from Janssen Pharmaceutical Ltd]. In addition, a crystalloid solution (sodium chloride 0.225 mol

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TABLE I. *Doses of propofol and alfentanil administered to groups 1–4 (series 1) and groups 5 and 6 (series 6)*

	Group					
	1 ($n = 8$)	2 ($n = 10$)	3 ($n = 8$)	4 ($n = 10$)	5 ($n = 12$)	6 ($n = 11$)
Propofol						
Initial dose (mg kg^{-1})	1	1.1	1.2	1.3	1.3	1.5
First 10 min (mg kg^{-1} h^{-1})	10	11	12	13	13	15
10–20 min (mg kg^{-1} h^{-1})	8	8.8	9.6	10.4	10.4	12
Final infusion (mg kg^{-1} h^{-1})	6	6.6	7.2	7.8	7.8	9
Alfentanil						
Initial dose (μg kg^{-1})	85	85	85	85	65	65
Infusion (μg kg^{-1} h^{-1})	65	65	65	65	50	50

litre^{-1} in 5% glucose) was infused through the cannula to ensure a continuous washin of the infusions, and to provide normal intraoperative fluid requirements.

A cannula was inserted into a vein on the dorsum of the hand and the adminstration set attached. Glycopyrronium 5 μg kg^{-1} was administered. Baseline recordings of heart rate (HR) and arterial pressure (AP) were made (Dinamap 1846, Critikon Ltd) when the heart rate had stabilized. The induction sequence began with the administration of all of the pre-calculated initial dose of alfentanil, followed by all of the pre-calculated initial dose of propofol. The infusions were immediately commenced and when it was established that the child was asleep, as assessed by loss of eye-lash reflex, suxamethonium 1 mg kg^{-1} was given to facilitate tracheal intubation. The initial dose of propofol was followed by a three-stage stepped infusion [15] commencing at induction and then decreased at 10 min intervals to the final, calculated rate on the 20th minute. This rate was maintained until the end of the procedure (table I). The child's lungs were ventilated with 100% oxygen until intubation, and thereafter with 30% oxygen in air to maintain the end-tidal partial pressure of carbon dioxide (PE'_{CO_2}) at 4.5–5.0 kPa. No inhalation agent was administered at this stage.

Continuous monitoring included ECG, pulse oximetry, capnometry and measurement of the inspired oxygen concentration. A ventilator alarm was in circuit. Arterial pressure and HR were recorded at 3-min intervals. Spontaneous return of neuromuscular function was confirmed with a nerve stimulator.

The child's motor response on incision of the skin and the time since induction were noted and a subsequent procedure (when deep dissection and traction were the usual causes), enflurane was added to the 30% oxygen in air mixture, in a concentration sufficient to suppress movement. Children were not given a non-depolarizing neuromuscular blocking drug or further increments of alfentanil or propofol, but the infusions were maintained at their pre-calculated rates.

At the end of surgery, the infusions of alfentanil and propofol were stopped simultaneously, and the time to tracheal extubation and the time to identify a simple item (a pen or watch) noted in children who were old enough to communicate. Where appropriate, 0.25% bupivacaine was used to provide a local block or caudal analgesia for postoperative pain relief, while the child was still anaesthetized.

Any unwanted effects which developed during induction, maintenance or recovery from anaesthesia were noted. The children and their parents were visited after operation the same evening, and again the following day. Any i.v. sequelae were noted, and those children who were old enough to talk (almost all) were asked specifically what they remembered of the procedure, if they had experienced any bad dreams or felt any pain during the operation. Parents and attending nursing staff were asked specifically about nausea and vomiting, and whether the child was well after operation.

At the end of the first series of patients, we questioned if the dose of alfentanil was inappropriately large (85 μg kg^{-1} loading dose followed by 65 μg kg^{-1} h^{-1}), and another two groups of patients (series 2, groups 5 and 6) were studied with a smaller loading dose of 65 μg kg^{-1} and infusion of 50 μg kg^{-1} h^{-1}. As it was anticipated that the propofol requirement would be greater in this second series (groups 5 and 6), we chose to give group 5 a dose of propofol which corresponded to the amount required to prevent 90% of patients moving, based on dose requirement calculations from the first series.

Analysis of propofol and alfentanil

Analysis of whole blood propofol was by high performance liquid chromatography [22] with fluorescence detection. The sensitivity of this assay in our laboratories is 0.1 μg ml^{-1}, with a coefficient of variation on the control samples included in each batch of 0.2%. That of plasma alfentanil was by radioimmunoassay using standards supplied by Janssen Pharmaceuticals. Again, the samples were analysed in batches. The sensitivity of the assay within the range used (100–300 ng ml^{-1}) was 10 ng ml^{-1}, with a coefficient of variation between batches of less than 5%.

Statistical analysis

Probit analysis using the SAS Statistical Analysis

TABLE II. *Patient age and weight, and time to incision (mean (range or* SD*))*

Group	Age (yr)	Weight (kg)	Time (min)
Series 1			
1	7.6 (3–11)	27.6 (9.4)	23.7 (13.0)
2	6.7 (4–12)	25.7 (6.3)	17.1 (5.0)
3	7.6 (4–12)	27.8 (9.5)	16.9 (6.7)
4	5.6 (3–11)	24.4 (10.0)	18.1 (8.4)
Series 2			
5	8.3 (4.5–12)	32.0 (8.2)	17.5 (3.1)
6	6.9 (3.5–11)	28.3 (6.9)	15.6 (4.1)

TABLE III. *Mean dose requirement of propofol (ED) and mean effective concentration of whole blood propofol (EC) at which 50% and 95% of the sample population show suppresion of response (ED_{50} and ED_{95}; EC_{50} and EC_{95} respectively), together with the respective 95% confidence limits. Series 1 = high-dose alfentanil; Series 2 = low-dose alfentanil*

	Series 1	Series 2
ED_{50} (mg kg^{-1} h^{-1})	6.0 (5.5–6.2)	7.5 (6.8–7.5)
ED_{95} (mg kg^{-1} h^{-1})	8.6 (8.0–9.2)	10.5 (9.6–13.1)
EC_{50} (µg ml^{-1})	1.71 (1.18–2.35)	1.92 (1.48–2.14)
EC_{95} (µg ml^{-1})	3.87 (2.76–7.38)	4.26 (3.74–8.22)

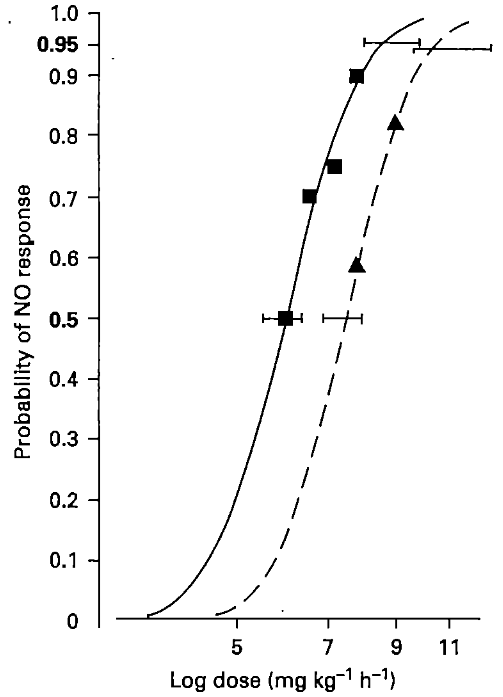

FIG. 1. Log dose (final infusion)–response curve based on the results from probit analysis of propofol requirement for children receiving high dose alfentanil (series 1, groups 1–4: ■——■) and low dose alfentanil (series 2, groups 5 and 6: ▲---▲). Also shown are the 95% confidence intervals (⊢—⊣) at ED_{50} and ED_{95}.

(EC) 50% and 95%), together with their 95% confidence intervals, were also calculated. The significance of differences between sample groups was determined by the Kruskal–Wallis test and by analysis of variance. Comparison between adult and paediatric data was by the unpaired Student's *t* test.

RESULTS

There were no significant differences in age, weight or time to incision either between the two series or between the six groups (table II). Table III

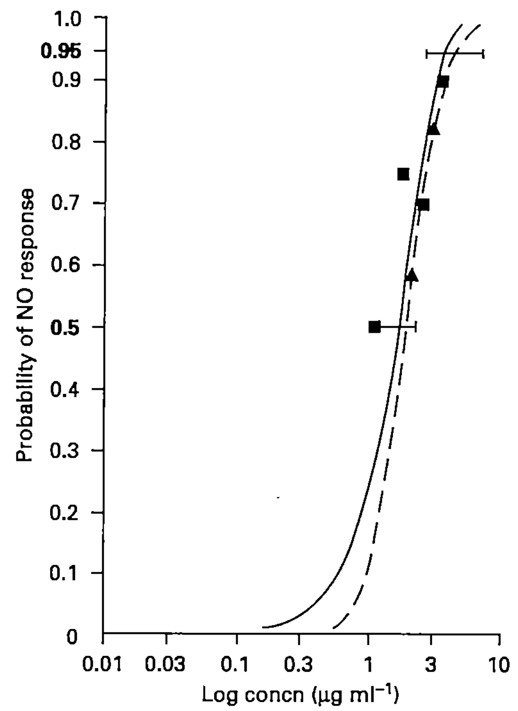

FIG. 2. Log concentration–response curve based on the results from probit analysis of whole blood propofol concentration for children receiving high dose alfentanil (series 1, groups 1–4: ■——■) and low dose alfentanil (series 2, groups 5 and 6: ▲---▲). Also shown are 95% confidence intervals (⊢—⊣) at ED_{50} and ED_{95}; as these are almost coincident, only one set of bars is displayed.

shows the calculated propofol dose requirement and calculated whole blood propofol concentration for 50% and 95% responses for each group.

Propofol dose–response and concentration–response

The results of the probit analysis for propofol dose–response and propofol concentration–response are shown in table III, and in figures 1 and 2, respectively. The final infusion rate of propofol required to suppress movement in 50% and 95% of children for both series 1 (groups 1–4) and series 2 (groups 5 and 6), together with the corresponding whole blood concentrations are shown in table III. The dose–response and concentration–response curves for series 2 are both parallel and to the right of those for series 1. This difference between the two series is significant only for the dose–response curve ($P < 0.005$) (fig. 1).

The results of the individual whole blood concentrations of propofol for movers and non-movers against dose administered, the means and SD for each of the groups and the regression line are shown in figure 3.

A multiple regression analysis conducted on the data in an attempt to determine what factors might be responsible in contributing to the concentration of propofol identified only the dose of propofol administered as being significant. Factors included in the analysis were patient weight and age, alfentanil dose, alfentanil concentration, propofol dose and time. Although the administered dose (represented by the final infusion rate) might be the most significant determinant of the resulting concentration, reference to figure 3 will confirm the wide

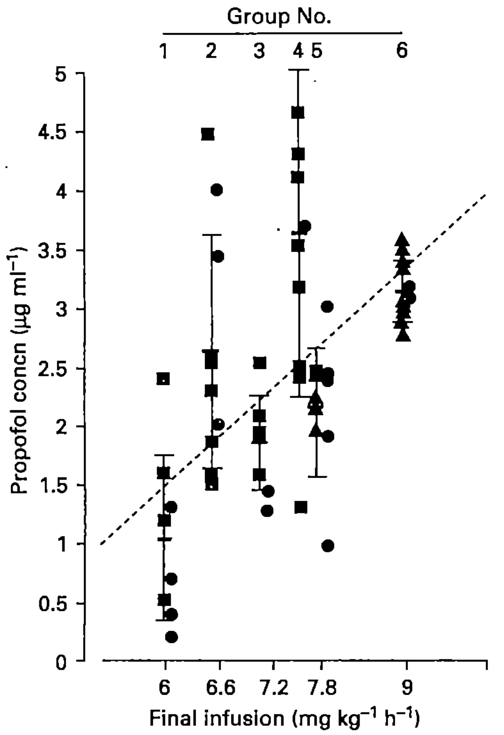

FIG. 3. Whole blood propofol concentration *vs* dose (represented by the final infusion rate) for groups 1 to 6 (mean, SD). ● = Patients from either series who moved; ■ = patients from series 1 who did not move; ▲ = patients from series 2 who did not move. The regression equation of the best fit line: propofol concentration = 0.57 (final infusion rate) −1.77 ($r = 0.55$; $P < 0.005$).

variation between the groups. The regression line shown, although a good predictor of the data ($P = 0.002$) has an r value of only 0.55. Outliers in groups 2 and 4, especially, account for the wide SD in these groups. More data are required to determine accurately the influence that alfentanil may have in affecting propofol concentration, for a given propofol infusion.

Alfentanil concentration

The alfentanil dosage scheme used in series 1 produced a mean plasma alfentanil concentration of 279 (SD 78) ng ml^{-1}. This was significantly greater ($P < 0.001$) than the values predicted from previous studies for adults [20]. In contrast, children in series 2 who received the smaller alfentanil infusion scheme had a mean plasma alfentanil concentration of 135 (SD 30) ng ml^{-1}, which although significantly less than that for series 1, was not significantly different to that achieved in the adult manual infusion schemes.

TABLE V. *Recovery times (mean (SD)) in 23 of the 59 children studied. Timed from the end of infusion, time to extubation = time at which the attending anaesthetist felt that adequate recovery of protective reflexes and ventilatory frequency had occurred; time to awake = time taken to identify a simple object.* **P < 0.05 compared with series 1*

	Series 1 (n = 13) (22%)	Series 2 (n = 10) (17%)
Time to extubation (min)	6.6 (2.3)	8.7 (2.6)
Time to awake (min)	13.2 (2.1)	16.8 (3.9)*

Haemodynamic data

There were no statistically significant changes in haemodynamic variables at any stage (table IV).

Recovery times

Of the 59 children entered into the study, 23 who had not received enflurane at any stage were monitored for the time taken to recovery. As fewer children in the groups who received a larger dose of propofol required supplementary enflurane, these results are biased to reflect the recovery times of those patients who might be expected to take longer to recover, principally groups 3–6. The time "awake" represents the time at which a common object was correctly identified (table V).

Side effects

Of the 59 children studied, 26 were noted to have some side effect, usually minor. The most severe reaction, seen in 11 children after loss of consciousness, was movement of one or both arms, usually heralded by a cough. Subsequently, alfentanil was administered in a divided dose: 50% of the calculated dose before the propofol and 50% after. This reduced the incidence and severity of movement in subsequent patients. Lignocaine was not added to the propofol, but only 11 children (19%) showed obvious retraction of the hand. Five children coughed almost immediately on injection of the alfentanil alone.

Two children complained of tenderness at the infusion site when visited after 24 h; both of these had received antibiotics in the postoperative period, through the same cannula. Only two children (3%) vomited in the postoperative period.

Most children (40) were able to remember getting on to the transport trolley in the ward. Three (3-yr-old) children were unable to understand the questions put to them. Eight patients had left the hospital

TABLE IV. *Alterations in haemodynamic response before induction (Before), after induction (but before surgery) (After), and within the first 10 min of surgery (During) (mean (SD) [range]). Haemodynamic data were recorded at 3-min intervals*

	Before	After	During
Heart rate (beat min^{-1})	91 (17.9) [54–129]	83 (15.2) [52–117]	80 (15.8) [56–124]
Mean change		−5	−5
SAP (mm Hg)	111 (10.0) [90–131]	100 (8.4) [81–115]	106 (9.8) [87–129]
Mean change		−2.7	−0.5
DAP (mm Hg)	61 (10.8) [36–82]	51 (9.1) [36–76]	60 (9.2) [44–83]
Mean change		−3.1	+0.8

before the second (24-h) follow-up. No child at any stage complained of any event which might be attributed to awareness, or any unpleasantness on going to sleep—even if they had retracted their hand, coughed or moved at the time, or at any stage during the maintenance or recovery from the anaesthetic.

DISCUSSION

We chose the somatic motor response (movement) of the patient to a standardized surgical stimulus, the skin incision, as the pharmacodynamic end-point in the same way as for the study of total intravenous anaesthesia in adults [5, 7–9], or the determination of minimum alveolar concentration (MAC) in adults [23, 24] and children [25]. Although there were minor variations in the exact site of incision, all incisions were confined to the lower abdomen, and represent an accepted "standard" surgical stimulus. Determination of the dose requirement of propofol was based on the same principles as those used in adults: several children within each group were exposed to the same dose of propofol (mg kg^{-1}), while alfentanil, at two different concentrations, was used to provide background analgesia analogous to the use of nitrous oxide in a standard inhalation technique.

We chose the combination of propofol and alfentanil because of their successful use in adults and their suitable pharmacokinetic profiles. Other agents, such as methohexitone and fentanyl, may be used in children, but dose requirement and recovery studies would be needed [26–28].

Reliable dose schedules for i.v. techniques are essential to provide an estimate of the smallest dose which may be compatible with adequate anaesthesia. As a sample size of nearly 60 children was tested at differing rates of infusion of propofol, an indication of the variability within the population may be obtained—the 95 % confidence limits about the ED_{50} or ED_{95}. An estimate of the potency of propofol can now be made in children, for comparison with adult data, from the steepness of the slope of the resulting dose requirement–response curve.

Alfentanil requirements

In order to allow comparisons with the adult data for the propofol–alfentanil total intravenous anaesthesia [9], we tried to predict the appropriate alfentanil dose based on the existing pharmacokinetic data in children [17–19]. We aimed to achieve a plasma alfentanil concentration comparable to that obtained in adults [20, 21], based on the premise that this would provide a comparable pharmacodynamic effect. The loading dose and infusion rate of alfentanil chose in series 1 was an overestimate (plasma alfentanil concentration 279 (SD 78) ng ml^{-1}) compared with previous findings (plasma alfentanil concentration 167 (SD 28) ng ml^{-1}) in adults given a loading dose of 50 μg kg^{-1} followed by an infusion of 50 μg kg^{-1} h^{-1} [20, 21]. The results obtained for series 2 (plasma alfentanil concentration achieved 135 (SD 30) μg ml^{-1}) were closer to the desired value. The differences in plasma concentration of alfentanil were not in proportion to the dose administered. A 23 % reduction in the alfentanil dose administered in series 2 reduced the alfentanil plasma concentration by more than 50 %, suggesting that alfentanil kinetics are not linear in the range studied, or that there may be a significant effect of propofol on alfentanil concentration, as these differences could not be attributed to differences in age or weight.

These findings emphasize the difficulty of predicting infusion requirements on the basis of pharmacokinetic data derived from single-dose kinetic studies [17–19].

Propofol requirement

The dose–response curves (fig. 1) for the two series were essentially parallel, but significantly displaced ($P < 0.005$) by 1.5 mg kg^{-1} h^{-1} at ED_{50} and by 1.9 mg kg^{-1} h^{-1} at ED_{95} (fig. 1). This almost parallel shift to the right in series 2, indicating an increased propofol requirement, was a result of the reduction of the alfentanil infusion alone.

The concentration–response curves (fig. 2) were almost superimposed, suggesting that the differences in the dose requirement in the two series were the result of other pharmacokinetic factors and not only differences in whole blood propofol concentration. The mean values for the whole blood concentrations were significantly smaller for a given infusion rate in series 2 compared with series 1, indicating that the greater infusion rates of alfentanil were causing an interaction to decrease the clearance or the steady-state volume of distribution of propofol, or both, resulting in greater whole blood concentrations of propofol in series 1. Possible alterations in liver blood flow or even a direct interaction of alfentanil with propofol may also have contributed to this effect.

Children compared with adults

When the dose requirements of children were compared with those of adults [14, 15] at a similar plasma alfentanil concentration (as achieved in series 2), the dose of propofol required to suppress movement in 95 % of the children studied was 10.5 mg kg^{-1} h^{-1}, double that required for adults (5.0 mg kg^{-1} h^{-1}) ($P < 0.001$). However, at this infusion rate the corresponding EC_{95} whole blood concentration of propofol was 4.62 μg ml^{-1} in children, which is similar to the EC_{95} found in adults (4.05 μg ml^{-1}). The ED_{50} requirement for children in series 2 was 7.5 mg kg^{-1} h^{-1}—again, more than double that for adults (2.94 mg kg^{-1} h^{-1}). The corresponding EC_{50} in the two groups were also similar: 1.92 μg ml^{-1} in children and 1.44 μg ml^{-1} in adults. Despite the variability in whole blood concentration in both adult and paediatric populations, these results are remarkably close, suggesting that, in the doses studied, propofol is more rapidly eliminated in children than in adults—an observation supported by Jones, Chan and Andrew [29].

Haemodynamic effects

Children anaesthetized with our propofol and alfentanil infusion schemes had little alteration in heart rate or systolic and diastolic arterial pressures. Although there were consistent decreases in each of these variables immediately after induction, these were small and similar to those observed with inhalation anaesthetic techniques using halothane [29–31]. The smallest systolic pressure observed was 81 mm Hg and the smallest diastolic 36 mm Hg, both of which occurred after induction in the same child. The average decrease in systolic pressure was about 3 mm Hg after induction, considerably less than the changes (−22% to −33%) observed in adults anaesthetized with a similar technique [6, 9, 16, 32, 33].

The average decrease in heart rate was about 5 beat min^{-1}, despite the administration of glycopyrronium. In one child (10 yr), the heart rate decreased to about 55 beat min^{-1}, where it remained for the duration of the anaesthetic. There was no obvious cause for this (ECG showed no heart block). We considered the use of glycopyrronium to be necessary, as the combination of alfentanil and propofol has been associated with bradycardia [16] and because the nature of the surgery had the potential to aggravate this further—for example, traction of the spermatic cord. However, children who have not been given atropine or glycopyrronium have demonstrated a similar haemodynamic stability when propofol was administered [12, 29].

Recovery

Children who had required supplementary enflurane were excluded from the assessment of recovery times. Caudal blocks were administered at the end of the procedure in an attempt to reduce any discomfort from the operation during the postoperative period. This would be likely to prolong the recovery times because of the "reduced" painful stimulus during recovery. The median time to extubation was 8 min (range 4–10 min) and represents the time at which spontaneous ventilation and protection of the airway was deemed adequate. The median time to response to command and recognition of a familiar object (possible in all of the 23 children studied) was 15 min (range 10–18 min). Surprisingly, despite a smaller dose of alfentanil in series 2, children took longer ($P = 0.013$) to wake up than those in series 1, presumably reflecting the larger dose of propofol, rather than an improvement which might have been anticipated from a reduced dose of alfentanil. These recovery times are similar to those in adults [9, 16, 29], but considerably shorter than the 30 min quoted by Jones, Chan and Andrew [29], whose patients had the benefit of a local anaesthetic block before surgery and received halothane for the maintenance of anaesthesia after induction with propofol.

Side effects

The constraints of gaining approval for this study did not allow us to add lignocaine to the loading dose of propofol. As the incidence of pain from injection of propofol in adults is about 40%, we expected that a large number of children might have complained of pain, and we therefore administered alfentanil before the propofol. However, cough and associated movement ("embrace" or "startle" reaction), even before the administration of propofol in six children from the first two groups, led us to alter the technique by administering 50% of the alfentanil, the initial propofol dose and then the remainder of the alfentanil. Only a further five children from the remainder of the study demonstrated this reaction, and then in a less extreme manner.

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PHARMACOKINETICS OF LIGNOCAINE IN CHILDREN AFTER INFILTRATION FOR CLEFT PALATE SURGERY

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SUMMARY

We have studied the pharmacokinetics of lignocaine in children after local infiltration for cleft palate surgery. After induction of anaesthesia, lignocaine 2.5 mg kg^{-1} with adrenaline 1:200000 was injected into the palate. Blood samples were collected before and at 2, 5, 10, 15, 20, 30, 60 and 120 min after infiltration. Plasma concentrations of lignocaine were measured by a gas–liquid chromatographic technique. There were no signs of systemic toxicity on routine monitoring of the patients and the peak plasma concentrations were less than the accepted toxic values. Mean half-life was 72.9 (SEM 9.9) min, similar to that found previously in adults and children. However differences in mean clearance (24.6 (2.04) ml kg^{-1} min^{-1}) and volume of distribution (0.80 (0.07) litre kg^{-1}) were found between this and previous studies. (Br. J. Anaesth. 1992; **69**: 577–579)

KEY WORDS

Anaesthesia: paediatric. Anaesthetic techniques: local infiltration. Anaesthetics, local: lignocaine. Pharmacokinetics.

The pharmacokinetics of lignocaine have been described in detail in several age groups [1, 2] and clinical applications [3–6]. Differences in plasma concentrations and pharmacokinetic variables have been shown in relation to age [4, 5, 7] and site of injection [3, 8–10].

Vasoactive agents, such as adrenaline, are used commonly in conjunction with lignocaine to provide local vasoconstriction resulting in decreased absorption, smaller peak plasma concentrations [11, 12] and prolongation of the duration of the local anaesthetic block [13, 14].

The palate is a highly vascular area and, in cleft palate surgery, it is our practice to use local infiltration with 0.5% lignocaine with 1:200000 adrenaline to minimize blood loss and provide analgesia during and after operation. It is likely that infiltration of lignocaine at this site leads to rapid absorption and large plasma concentrations. However, no data are available describing lignocaine pharmacokinetics after injection at this site.

The aim of this study was to determine the pharmacokinetics of lignocaine after infiltration for cleft palate surgery.

PATIENTS AND METHODS

After obtaining Ethics Committee approval and written, informed consent by parent or guardian, we studied 10 ASA I and II patients presenting for elective cleft palate surgery.

Premedication (trimeprazine 2 mg kg^{-1}) was given only to patients older than 1 yr. Anaesthesia was induced with either an inhalation or an i.v. technique, depending on the assessment of the patient's airway and the availability of i.v. access. Inhalation induction was performed with 70% nitrous oxide and 0.5–3% halothane in oxygen and i.v. induction consisted of thiopentone 5 mg kg^{-1}. After induction of anaesthesia, neuromuscular block was produced with suxamethonium 1 mg kg^{-1} and the trachea was intubated. Anaesthesia was maintained by intermittent positive pressure ventilation using 70% nitrous oxide and 0.5–1% halothane in oxygen. Neuromuscular block was maintained by incremental doses of atracurium and intraoperative analgesia by i.v. morphine 0.1 mg kg^{-1}, administered immediately after induction of anaesthesia.

Intraoperative monitoring consisted of continuous ECG, peripheral oxygen saturation (Sp_{O_2}), peripheral temperature, non-invasive arterial pressure (AP) estimations at 3-min intervals and auscultation of breathing and heart sound by precordial stethoscope.

At the end of anaesthesia, residual neuromuscular block was antagonized using neostigmine 50 µg kg^{-1} preceded by atropine 20 µg kg^{-1}. After spontaneous ventilation had returned, the trachea was extubated and the patient taken to the recovery ward.

After induction of anaesthesia and before commencement of surgery, the surgeon infiltrated the patient's palate using 0.5% lignocaine hydrochloride 0.5 ml kg^{-1} (2.5 mg kg^{-1}) with adrenaline 1:200000. Several injections were made into the palate, preceded by aspiration to reduce the risk of accidental intravascular administration. All infiltrations and operations were performed by the same surgeon. Venous blood samples (1 ml) were collected before infiltration and at 2, 5, 10, 15, 20, 30, 60 and 120 min

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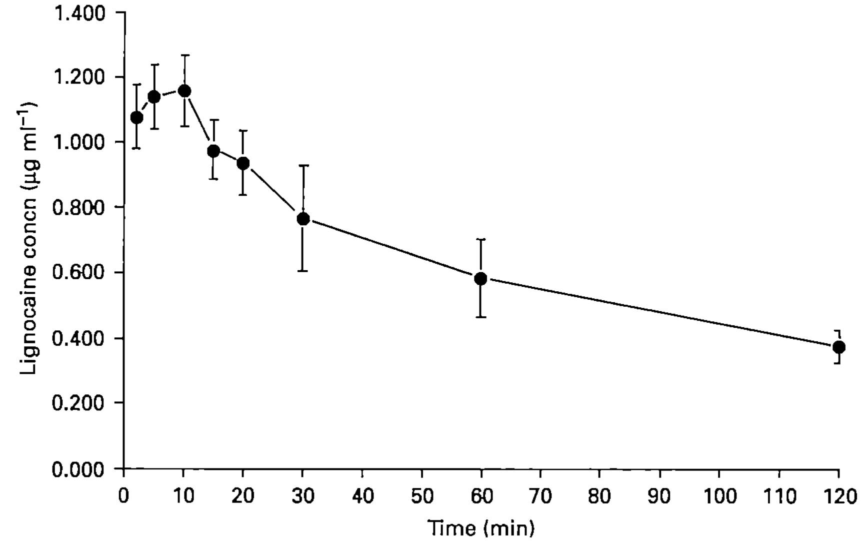

FIG. 1. Mean (SEM) plasma lignocaine concentrations after infiltration for cleft palate surgery.

after infiltration. The samples were collected from an i.v. cannula inserted into an antecubital vein after induction of anaesthesia, in the arm contralateral to that used for the injection of anaesthetic drugs. After collection, the blood was centrifuged and the plasma separated and frozen at −20 °C until required for analysis.

Lignocaine concentrations were measured using gas–liquid chromatography with an FTD (N_2) detector. A plasma sample aliquot was made basic with sodium hydroxide and extracted with toluene. Etidocaine was used as the internal standard. After mixing, the samples were centrifuged and 5–10 μl of the extract injected into the column. A 2-m column packed with 3 % OV17 on GCQ support was used at 220 °C, with interior and detector temperatures of 260 °C. Calibration of the method was linear to 20 μg ml^{-1} with a lower limit of detection of 0.2 μg ml^{-1}. Intra-assay variation was less than 2.8 % at all points, with an extraction efficiency of 93 % and inter-assay variation of 1.7 %.

From the measured plasma concentrations, using standard pharmacokinetic equations and the microcomputer program PHARM-PCS (MicroComputer Specialists, Version 4), the following variables were calculated for each patient: area under the time–concentration curve to infinity (AUC), first moment of AUC (AUMC), elimination constant (k_{10}), elimination half-life ($T_{\frac{1}{2}} = 0.693/k_{10}$), volume of distribution at steady state (Vd^{ss} = dose $\times$(AUC)²/AUMC) and total plasma clearance (*Cl* = dose/AUC).

Maximum concentration (*C*max) and time to maximum concentration (*tC*max) were calculated from the plasma concentration *vs* time data.

RESULTS

Mean (range) age and weight were 39.7 months (8–90 months) and 14.5 kg (7.1–27 kg), respectively. Mean (range) duration of surgery was 49.8 min (32–68 min) and mean (range) dose of lignocaine 35.75 mg (17.5–67.5 mg).

Heart rate (HR), arterial pressure and oxygen saturation were not affected after infiltration with lignocaine and adrenaline. The ECG showed no changes in rhythm or morphology during surgery in any patient.

Figure 1 shows the mean (SEM) plasma lignocaine concentration *vs* time curve. Mean (SEM) calculated pharmacokinetic values were: half-life ($T_{\frac{1}{2}}$) 72.7 (9.1) min; clearance (*Cl*) 24.6 (2.04) ml kg^{-1} min^{-1}; volume of distribution (*V*d) 0.8 (0.07) litre kg^{-1}; maximum concentration (*C*max) 1.27 (0.13) μg ml^{-1}; time to maximum concentration (*tC*max) 6.3 (1.5) min.

DISCUSSION

Lignocaine infiltration in this study did not result in large concentrations in the plasma. The mean and individual maximum concentrations were 1.3 μg ml^{-1} and 2.1 μg ml^{-1}, respectively, considerably less than the quoted minimum toxic concentration of 5 μg ml^{-1} [15, 16].

As all the monitored variables (HR, AP, Sp_{O_2} and ECG) remained unchanged, it is likely that inadvertent i.v. injection of lignocaine with adrenaline did not occur. The slow increase in plasma concentrations of lignocaine in all the patients confirms this.

The elimination half-life of 72 min found in this study is similar to that described in adults [16] and in children after i.v. lignocaine [1]. A longer half-life was found in children after caudal lignocaine by Ecoffey and colleagues [4], who suggested that this was the result of a larger volume of distribution. Although half-life can be prolonged as a result of a decrease in clearance caused by halothane anaesthesia as shown by Bentley, Glass and Gandolfi [17], the clearance in the present study was much greater than previous investigators have found in children [1, 4]. As the calculation of clearance is inversely related to AUC and therefore plasma concentrations for a given dose, a reduction in the measured plasma concentrations would lead to a large clearance value. A possible explanation for small measured plasma concentrations is that lignocaine undergoes local breakdown before absorption, as suggested by

Barone and co-workers [18], who found no detectable serum lignocaine after local infiltration for suturing of wounds using doses of up to 300 mg. In addition, a proportion of the lignocaine dose may not be absorbed as a result of blood loss caused by surgery in the infiltrated area.

Volume of distribution in this study was similar to that in adults as found by Tucker and Mather [19], but much smaller than that in children [4]. Volume of distribution may be expected to be greater in children as a result of the larger percentage of water as body weight [7].

Absorption of lignocaine from mucous membranes is rapid and can result in toxic plasma concentrations in children receiving topical tracheal lignocaine [5]. However, this did not occur in the 10 patients in this study, in whom lignocaine was used in combination with adrenaline for infiltration of the palate, or in previous studies in which lignocaine gel and solution were applied to the nasopharynx and mouth [9, 10].

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PHARMACOKINETICS OF MIVACURIUM IN NORMAL PATIENTS AND IN THOSE WITH HEPATIC OR RENAL FAILURE

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SUMMARY

We have determined the pharmacokinetics and duration of action of a bolus dose of mivacurium (0.15 mg kg^{-1}) during isoflurane and nitrous oxide anaesthesia in nine patients with normal renal and liver function, nine patients undergoing cadaveric kidney transplantation and nine patients undergoing cadaveric liver transplantation. Total plasma concentrations of mivacurium were measured for 2.5 h after administration using a high-pressure liquid chromatographic assay. Plasma concentration vs *time data for what were presumed to be the two active mivacurium isomers were analysed by a non-compartmental method based on statistical moments. Neuromuscular block was assessed by measuring the electromyographic evoked response of the adductor pollicis muscle to train-of-four stimulation of the ulnar nerve. The mean time to recovery of 25% neuromuscular transmission,* T_{25}, *was greater in the patients with liver failure (57.2 min) than in control patients (18.7 min). The volume of distribution at steady rate* (Vd^{ss}) *was comparable in the three groups. Patients with impaired liver function had significantly longer mean residence time and smaller plasma clearance than did patients with renal failure or control patients. There were significant negative correlations between plasma cholinesterase activity and both* T_{25} ($r = 0.79$) *and mean residence time* ($r = 0.62$). (Br. J. Anaesth. 1992; **69**: 580–585)

KEY WORDS

Enzymes: plasma cholinesterase (butyrylcholinesterase). Kidney: renal failure. Liver: hepatic failure. Neuromuscular relaxants: mivacurium. Pharmacokinetics: mivacurium.

Mivacurium, a potent short-acting non-depolarizing neuromuscular blocking agent, consists of three stereoisomers: *trans–trans* (57.4% w/w), *cis–trans* (36.2% w/w), and *cis–cis* (6.4% w/w). The *cis–cis* isomer may be considered to be pharmacologically inactive [unpublished data Burroughs Wellcome Company]. The short duration of action of mivacurium is in large part related to its hydrolysis by butyrylcholinesterase (plasma cholinesterase) [1, 2]. Hydrolysis of mivacurium produces a quaternary monoester, a quaternary amino alcohol and a dicarboxylic acid. These breakdown products are pharmacologically inactive. Hepatic or renal elimination of mivacurium may also play a role in determining the duration of action of mivacurium. This study was designed to evaluate the pharmacokinetics and pharmacodynamics of mivacurium in adults with normal kidney and liver function and in adults with either kidney or liver failure.

PATIENTS AND METHODS

We studied 27 surgical patients, (20 men) aged 20–59 yr allocated to three groups. The study was approved by the hospital's Institutional Review Board, and informed written consent was obtained from each patient. Nine patients (ASA class III or IV) had end-stage liver disease and were to undergo cadaveric hepatic transplantation, nine patients (ASA class III) with end-stage renal disease were to undergo cadaveric renal transplantation, and nine patients (ASA class I or II) without known hepatic or renal disease served as controls. The liver and renal transplants were performed on an urgent basis. No patient in the liver transplantation group had overt preoperative renal failure, although glomerular filtration rate was not assessed; the greatest serum creatinine concentration was 190 μmol litre^{-1}. All patients with renal failure underwent dialysis within the 48 h preceding transplantation. No patient received aminoglycoside antibiotics or antihistamine drugs within 48 h of the study, and none had any disease known to affect neuromuscular transmission. Average age, weight and selected laboratory data for the three groups are summarized in table I. Plasma cholinesterase and dibucaine inhibition were determined by a commercial laboratory using a standard spectrophotometric technique with acetylcholine chloride as a substrate. Blood for these

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TABLE I. *Patient and preoperative laboratory data (mean (range or SD)). Significant differences* ($P < 0.05$) *compared with value in : * control patients ; † hepatic failure patients. AST = Aspartate aminotransferase ; ALT = alanine transaminase ; GGPT = γ-glutamyl pyruvic transaminase*

	Control patients ($n = 9$)	Patients with hepatic failure ($n = 9$)	Patients with renal failure ($n = 9$)	Normal values
Age (yr)	26.9 (21–35)	42.2 (22–59)	34.0 (27–41)	—
Weight (kg)	77.3 (11.9)	74.1 (16.9)	73.7 (11.7)	—
PCV (%)	39.8 (4.6)	32.6 (5.4)	29.1 (8.6)*	37–52
Plasma urea (mmol litre^{-1})	2.2 (0.8)	3.3 (0.15)	10.6 (2.4)*†	1.7–3.3
Creatinine (μmol litre^{-1})	84.5 (16.9)	101.4 (42.3)	1259 (464.7)*†	59.2–118.3
Alkaline phosphatese (iu ml^{-1})	51.1 (14.5)	228.5 (212.0)	122.4 (102.6)*	30–105
AST (iu ml^{-1})	19.4 (7.4)	271.5 (364)*	18.1 (12.9)	7–40
ALT (iu ml^{-1})	18.5 (9.4)	138.9 (187)	24.8 (16.4)	0–41
Bilirubin (μmol litre^{-1})	0.7 (0.2)	12.7 (12.3)*	0.6 (0.2)†	0.2–1.3
Albumin (g litre^{-1})	39 (2)	26 (6)*	38 (4)†	35–50
GGPT (iu ml^{-1})	15.6 (8.0)	116.4 (138.8)*	39.3 (31.7)	7–52
Plasma cholinesterase (iu ml^{-1})	4.9 (1.3)	1.4 (0.9)*	4.9 (1.5)†	2.5–7.1
Dibucaine number (% inhibition)	82.9 (1.2)	67.4 (12.4)*	83.0 (3.7)†	77–83

studies was obtained before the administration of suxamethonium.

Anaesthesia was induced with thiopentone 3–10 mg kg^{-1} and tracheal intubation was facilitated by the administration of suxamethonium 0.9–2.6 mg kg^{-1}. Anaesthesia was maintained during the study period with 0.5–0.8 % isoflurane (end-tidal concentration) and nitrous oxide in oxygen and incremental doses of fentanyl 1–18 μg kg^{-1}, if needed. Ventilation was controlled to maintain end-tidal $P\text{CO}_2$ between 4.6 and 5.3 kPa. Arterial pressure was monitored directly with an indwelling radial arterial cannula. Body temperature was maintained at 35.0–37.5 °C.

After induction of anaesthesia, neuromuscular function was monitored by supramaximal stimulation of the ulnar nerve at the wrist with repetitive train-of-four (TOF) stimuli (2 Hz for 2 s at 10-s intervals) using surface electrodes. The evoked compound electromyogram (EMG) of thumb adduction (adductor pollicis) was recorded using a Datex monitor. After full recovery of neuromuscular transmission from suxamethonium and re-establishment of a baseline evoked response, a single bolus injection of mivacurium 0.15 mg kg^{-1} was administered through a peripheral i.v. catheter over 5 s. The amplitude of the first (T1) TOF response was used to quantity the degree of neuromuscular block which was expressed as a percentage of the baseline T1 response. The time to maximum block, the maximum degree of block and the times for the T1 response to return to 5 % (T_5), 25 % (T_{25}), 75 % (T_{75}) and 95 % (T_{95}) after the initial injection of mivacurium were recorded. The recovery index (T_{25-75}) was calculated from these data. Recovery was referenced to final baseline (maximum T1 obtained). At T_{95} in 16 patients, an appropriate bolus dose of either tubocurarine or pancuronium was administered to provide neuromuscular block for the remainder of the surgical procedure. EMG recording in one liver transplant patient was prevented by electrical interference; EMG data for one control patient were excluded from analysis because the study procedure was not adhered to.

Arterial blood samples (5 ml) were obtained at 1, 3, 4, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90 and 150 min after the dose of mivacurium. The blood samples were transferred immediately into tubes containing EDTA and 0.4 ml of 0.25 % phospholine iodide (a mixed cholinesterase inhibitor). The contents were mixed and centrifuged, and the plasma was decanted and stored at −60 °C. Urine was collected from an indwelling urinary catheter for 6 h for estimation of renal excretion and clearance of mivacurium in nine patients undergoing liver transplantation and four patients acting as controls.

Total mivacurium concentrations in plasma and in aliquots of urine were measured later by reversed phase, high pressure liquid chromatography (HPLC) with ultraviolet detection using doxacurium as the internal standard [3]. The concentrations of the quaternary monoester and the quaternary amino alcohol in urine were measured by a separate HPLC assay. Briefly, mivacurium was extracted from plasma by solid phase extraction on C-1 reversed phase cartridges. Doxacurium 200 ng, the internal standard, was added to mivacurium plasma samples (1 ml) before sequential washes. Eluted extracts were analysed using a Varian 5060 HPLC. The coefficient of variation was 1.7–2.1 % over the concentration range 10–1000 ng ml^{-1}. The limit of sensitivity of the assay was 10 ng ml^{-1}. Mivacurium and metabolites were extracted from acidified urine (pH 4.0) by solid phase extraction on C-1 cartridges and the samples were washed sequentially. A Hewlett-Packard 1090 HPLC system was used in conjunction with a Hewlett-Packard 1040 photo-diode array detector to analyse eluted urine extracts. A RP-Spherisorb C-1 column was used for separations. Various mobile phases were used for mivacurium and its metabolites. The coefficient of variation for the monoester metabolite and the quaternary alcohol metabolite was 5.5–18.5 % over a concentration range of 1–40 μg ml^{-1}.

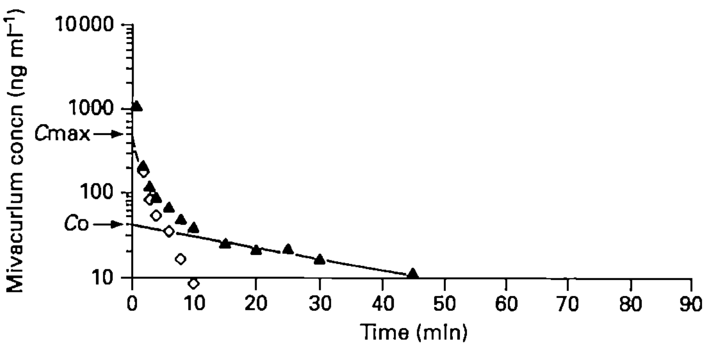

Fig. 1. Total mivacurium concentration (▲) and *cis–trans* and *trans–trans* isomer concentration (◇) in a typical patient. The contribution of the *cis–cis* isomer to the total measured concentration of all isomers of mivacurium was estimated by back extrapolation of the terminal elimination curve to time zero. This assumes that the terminal phase represents the *cis–cis* isomer. *Co* = estimated concentration of *cis–cis* mivacurium at time zero; *Cmax* = estimated concentration of active mivacurium at time zero.

Table II. *Cis–cis mivacurium pharmacokinetic parameters (mean* (SD))

Parameter	Control patients ($n = 8$)	Patients with hepatic failure ($n = 9$)	Patients with renal failure ($n = 9$)
Co (ng ml^{-1})	61.9 (29)	138.0 (84.2)	48.5 (11.2)
k (litre min^{-1})	0.048 (0.029)	0.022 (0.007)	0.032 (0.019)
$T_{\frac{1}{2}}$ (min)	18.4 (8.2)	34.3 (30.8)	34.3 (13.0)

Table III. *Onset time (time to maximum neuromuscular block), maximum block and duration of action of mivacurium in patients with or without organ failure (mean* (SD)). *Significant differences* ($P < 0.05$) *compared with value in*: * *control patients*; † *hepatic failure patients*

Neuromuscular variables	Control patients ($n = 8$)	Patients with hepatic failure ($n = 8$)	Patients with renal failure ($n = 9$)
Onset time (min)	1.9 (1.0)	2.1 (0.9)	2.6 (0.9)
Maximum block (%)	99.8 (0.7)	100 (0)	100 (0)
T_{25} (min)	18.7 (6.2)	57.2 (18.6)*	30.1 (12.8)
Recovery index (T_{25-75}) (min)	5.5 (2.5) ($n = 7$)	15.7 (9.3)* ($n = 5$)	11.5 (3.6) ($n = 8$)
T_{95} (min)	27.4 (10.8) ($n = 7$)	86.3 (44.2)* ($n = 5$)	51.0 (15.5) ($n = 7$)

The plasma concentrations of mivacurium were used to construct plasma concentration–time profiles for the drug. The pharmacokinetic and pharmacodynamic data for one patient were eliminated from the control group because the plasma samples were partially lost during processing. The pharmacokinetic data were analysed initially by both model-dependent and model-independent methods. A computer adaptation of a manual graphic technique for exponential stripping, CSTRIP, was used to obtain initial polyexponential estimates. The decay curves were fitted from the i.v. data using both two-compartment and three-compartment models with a non-linear least-squares regression microcomputer program, MULTI, using a modified non-weighted Marquardt algorithm. The residual sum of squares was reduced significantly by addition of a third compartment in 16 of 26 patients. Goodness-of-fit estimates confirmed these findings. Model-independent pharmacokinetic parameters of mean residence time (MRT), clearance (*Cl*), and volume of distribution at steady state (Vd^{ss}) were determined using standard formulae based on statistical moment theory [4]. MRT, the statistical moment analogous to half-life ($T_{\frac{1}{2}}$), represents the time for 63.2 % of an administered dose to be eliminated. Elimination was assumed to take place from the central compartment. The area under the curve (AUC) from time zero to time infinity was estimated by conventional linear trapezoidal summation and from the exponential extrapolation of the slope of the terminal phase. The AUC at the last data point represented 92 % (SD 5 %) of the estimated AUC at infinity. Total *Cl* was calculated by dividing the dose by AUC.

The pharmacokinetic half-life of a drug may be estimated from observations of effect [5, 6]. Briefly, doubling the dose of drug produces a duration of action that is prolonged by the elimination half-life of the drug. Preliminary review of the pharmacokinetic data revealed a long terminal elimination half-life an order of magnitude greater than that predicted from the increase in duration of neuromuscular block seen from doubling the dose in our other clinical studies [7, 8]. Further studies demonstrated that the *in vitro* plasma hydrolysis rate of the essentially inactive *cis–cis* isomer is significantly slower than that of the pharmacologically active *cis–cis* and *trans–trans* isomers.

Subsequent HPLC analysis of selected samples using a newly developed stereospecific assay showed that the terminal phase represents primarily the *cis–cis* isomer. In the new assay, mivacurium isomers together with an analogue of mivacurium as an internal standard were isolated from plasma by solid phase extraction with C18 and anion exchange cartridges. The eluted extracts were analysed by reversed phase HPLC with an RP select B column and fluorescence detection. The retention times of the *trans–trans*, *cis–trans* and *cis–cis* isomers and the internal standards in this system were 8.4, 9.3, 10.2 and 13.1 min, respectively. The assay was linear over the concentration range 5–250 ng ml^{-1}; the coefficient of variation for the three isomers was 3–6 %. Insufficient quantities of plasma remaining from the present study precluded re-analysis of most samples. Consequently, we corrected the plasma

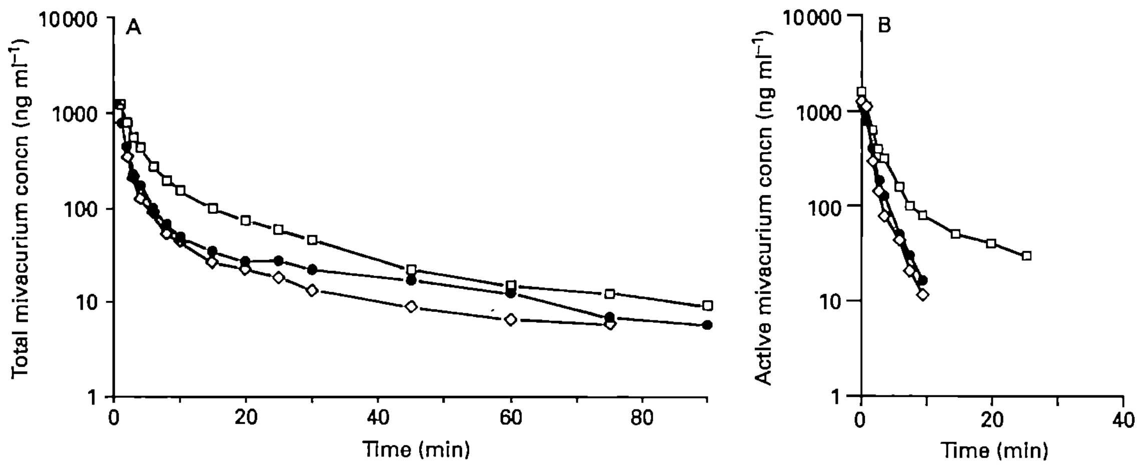

FIG. 2. A: Total mivacurium concentration (all three isomers) *vs* time curves in patients with liver failure (□) or kidney failure (●) and in control patients (◇). B: Concentrations of *cis–trans* and *trans–trans* isomers in same patients groups.

concentration–time profiles by assuming that the terminal phase of the profile represented the disposition of the *cis–cis* isomer for that patient.

A graphical curve-stripping program was used to obtain the slope and intercept (*C*o) for the terminal phase for each patient. These parameters were used to subtract the presumed contribution of the *cis–cis* isomer from each plasma concentration–time data point and to estimate the time zero (*C*max) concentration of the active isomers (fig. 1). The extrapolated time zero concentration (*C*o), the first-order rate constant (*k*), and $T_{\frac{1}{2}}$ values for the *cis–cis* isomer were noted (table II). One assumption of this method is that the *cis–cis* isomer obeys a one-compartment model; therefore, this model does not account for the distribution of the *cis–cis* isomer. The estimated *C*o *cis–cis* mivacurium concentration averaged 6.5 (SD 4.7) % of the estimated total mivacurium concentrations. Plots of average total mivacurium concentrations and calculated *cis–trans* and *trans–trans* isomer concentrations (fig. 2) further illustrate the differences between measured and corrected concentration–time profiles for the three treatment groups. These newly estimated plasma concentrations of mivacurium were used to construct new plasma concentration–time profiles for the drug. Model-independent pharmacokinetic parameters were recalculated. The dose of mivacurium was assumed to be 140.5 µg kg^{-1} (based on the amount of active isomers in the clinical trial material).

A one-way analysis of variance was performed to evaluate differences in the calculated parameters between the three groups. Statistical significance was assumed at $P \leqslant 0.05$.

RESULTS

There was no significant difference in the degree of neuromuscular block or the onset time of maximum neuromuscular block after mivacurium 0.15 mg kg^{-1} between the three groups of patients. The time from administration of drug to T_{25} and T_{95}, and the T_{25-75} index were greater in the patients with liver failure than in the control patients. There were no differences in these values between the patients with renal failure and control patients (table III). The T_{25} and T_{95} recovery times were less in renal failure patients than in liver failure patients.

TABLE IV. *Pharmacokinetic parameters of pharmacologically active mivacurium isomers (mean* (SD)). *Significant differences* ($P < 0.05$) *compared with value in: * control patients (ANOVA); † hepatic failure patients. AUC = Area under the concentration–time curve;* Cl = *clearance;* V*d*^{ss} = *volume of distribution at steady state; MRT = mean residence time*

Parameter	Control patients ($n = 8$)	Patients with hepatic failure ($n = 9$)	Patients with renal failure ($n = 9$)
AUC (ng min ml^{-1})	2273 (864)	4868 (1847)*	2390 (1225)
Cl (ml kg min^{-1})	70.4 (28.1)	33.3 (13.8)*	76.6 (43.6)†
*V*d^{ss} (ml kg^{-1})	112 (72)	124 (52)	150 (122)
MRT (min)	1.5 (0.8)	4.2 (2.6)*	1.9 (0.5)

Mean total mivacurium concentration and active isomer concentration (determined by correction) *versus* time data for the three patient groups indicate that, 15 min after administration of mivacurium, active isomers of mivacurium were no longer present in plasma from any control patient or any patient with renal failure; the mean plasma concentration of mivacurium in the patients with hepatic failure had declined to about 95 % of the maximum concentration by 30 min (fig. 2). The AUC to the last data point was nearly equal to the total area at infinity. By 90 min, only three liver transplant patients had detectable concentrations of mivacurium. The mean percentage (SD) of the mivacurium dose recovered unchanged in the urine from control patients and patients with liver failure was 7.1 (4.9) %. The mean percentages of monoester metabolite and quaternary alcohol metabolite (expressed as mivacurium molar equivalents) were 43.6 (28.9) % and 46.4 (34.3) %, respectively.

Model-independent pharmacokinetic data for the active isomers for the three patient groups are summarized in table IV. Patients with impaired liver function had significantly greater AUC and MRT, but smaller *Cl* than did patients with renal failure or control patients. *V*d^{ss} did not differ significantly between the three groups. There was a significant negative, non-linear correlation between plasma cholinesterase activity and T_{25} ($r = 0.79$) (fig. 3) and

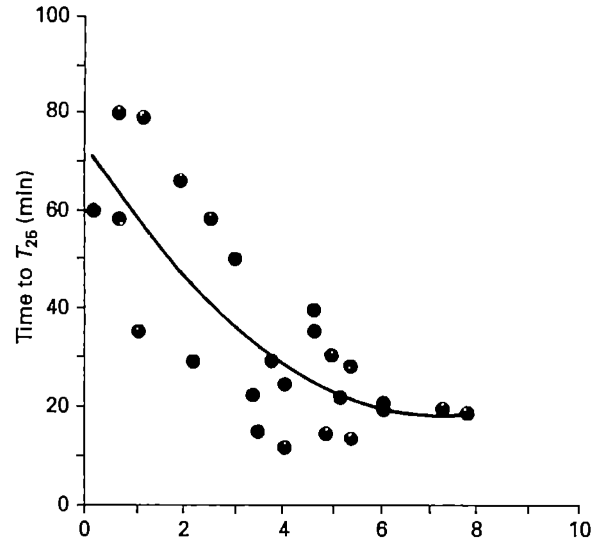

FIG. 3. Time to 25% recovery of neuromuscular transmission (T_{25}) as a function of plasma cholinesterase activity in all patients. Data are described better by a hyperbola ($r = 0.79$; $P < 0.05$; standard error of estimate = 12.9) than by a straight line ($r = 0.75$, $P < 0.05$, standard error of estimate = 13.7). The residual sum of squares was reduced by the addition of the power function.

a significant negative linear correlation between plasma cholinesterase activity and MRT ($r = 0.62$). There was no correlation between serum albumin concentration or plasma cholinesterase activity and Vd^{ss}.

DISCUSSION

This study was designed to evaluate the influence of either hepatic failure or renal failure on the pharmacodynamics and pharmacokinetics of mivacurium. The dose of mivacurium used (0.15 mg kg^{-1}) was estimated to be about twice the ED_{95} for neuromuscular block during nitrous oxide–isoflurane anaesthesia. This dose of mivacurium produced complete neuromuscular block in nearly all patients in the three groups. The times to onset of maximum mivacurium-induced block were similar in patients with liver or kidney failure and control patients. The ED_{95} of a neuromuscular blocker is the product of the Vd^{ss} and the plasma concentrations associated with that degree of neuromuscular block ($C_P{}^{ss}{}_{95}$). Pathophysiological changes associated with hepatic or renal disease frequently alter plasma cholinesterase activity, protein binding and volumes in which drugs distribute [9–11]. Renal dialysis can also influence drug distribution and plasma cholinesterase activity. Vd^{ss} was similar in the three patients groups and was nearly equal to the extracellular fluid volume; it did not correlate with serum albumin concentration or plasma cholinesterase activity.

The patients with liver failure exhibited markedly longer durations of neuromuscular block than did those with kidney failure or those with normal liver and kidney function. The T_{25} and T_{95} were prolonged and more variable in the hepatic failure group compared with the control group. In addition, the liver failure group had a prolonged T_{25-75} and a smaller plasma cholinesterase activity. There was also a significant inverse relationship between plasma cholinesterase activity and T_{25} in this group. Thus the longer clinical duration of neuromuscular block in patients with liver failure may be explained largely by the decreased plasma cholinesterase activity. However, other factors influencing the duration of block (for example pharmacodynamic changes), cannot be excluded. The duration of mivacurium-induced block was slightly longer in patients with kidney failure than in control patients. This finding is not fully explained by the pharmacokinetics.

The analysis of the pharmacokinetic data was initially complicated by the presence of the three stereoisomers of mivacurium in the drug formulation and the lack of stereospecific assays for these isomers. The ED_{95} for neuromuscular block of the *cis–cis* isomer is about 10-fold greater than that of the other two isomers. Because the *cis–cis* isomer is markedly less potent and accounts for only 6% of the administered dose, its contribution to the neuromuscular block produced by mivacurium is negligible. Initially, concentrations of individual isomers could not be separated by the assay. Preliminary plots of mivacurium plasma concentration *vs* time revealed a long, relatively slow terminal elimination phase that was not consistent with the short clinical duration of the drug, clinical predictions of the half-life, or *in vitro* predictions of the half-life [1, 2]. These inconsistencies were largely resolved with the development of a stereospecific assay. The stereospecific assay demonstrated that the *in vitro* hydrolysis half-lives of the *cis–trans*, *trans–trans* and *cis–cis* isomers in human plasma were 1.4, 1.8 and 22 min, respectively. The half-lives for the *cis–trans* and *trans–trans* isomers in human plasma are comparable to those reported by Cook and colleagues [2]. In their assay, however, the slowly metabolized *cis–cis* isomer was fortuitously removed by manipulation of the HPLC solvent flow.

The volume of distribution of mivacurium is comparable to that of other non-depolarizing neuromuscular blockers. However, the clearance values for mivacurium in normal patients (70 µg kg^{-1} min^{-1}) are at least 10-fold greater than the clearance values for other non-depolarizing blocking drugs (atracurium at 6 µg kg^{-1} min^{-1} or vecuronium at 5 µg kg^{-1} min^{-1}) [12, 13]. The clearance values for mivacurium most probably reflect rapid enzymatic degradation. We found that mivacurium was eliminated more slowly from the plasma of patients with liver failure. Consequently, mivacurium plasma concentrations in these patients were greater for all time periods than those in the other groups of patients. Our data show that about 7% of an administered dose of mivacurium was excreted unchanged in the urine within 6 h. As most patients in whom renal excretion of mivacurium was measured had liver disease, these data may overestimate the renal excretion of mivacurium in normal patients. Renal excretion of unchanged mivacurium is a minor elimination pathway.

Reduced plasma cholinesterase activity rather than organ failure *per se* was probably responsible for the prolonged clinical duration, prolonged MRT and reduced clearance of mivacurium in some patients. Patients with liver failure had extremely little enzyme activity associated with dibucaine numbers between 50 and 83. All patients seemingly had genotypically normal enzyme; dibucaine numbers were appropriate for the plasma cholinesterase activity. In general, the smaller the enzyme activity the smaller the dibucaine number. In our view, this finding reflects the homozygous normal genotype rather than the heterozygous condition, although we cannot exclude the latter possibility. No patient had a dibucaine number less than 30. No further characterization of plasma cholinesterase genotypes was performed. The duration of neuromuscular block produced by mivacurium increased with decreasing plasma cholinesterase activity. Similar findings have been noted by others for suxamethonium [7–10].

Diminished activity of plasma cholinesterase, a glycoprotein produced in the liver, may be caused by physiological variation (age or pregnancy), disease, iatrogenic or environment change and genetic alteration [9–11, 14–19]. In 50–70 % of all patients with a prolonged liver disease such as hepatitis, liver abscess or cirrhosis, there is marked reduction in plasma cholinesterase activity. A reduction to 25–50 % of normal is not uncommon. Indeed, eight of our nine patients with liver failure had plasma cholinesterase activities less than normal. In general, reduced plasma cholinesterase activity was associated with reduced serum albumin concentration. Patients with acute or chronic renal disease may also show diminished plasma cholinesterase activity, presumably because of reduced hepatic synthesis. In such patients the range of plasma cholinesterase activity varies between 25 and 100 % and the activity is often reduced by 30–55 %. Chronic dialysis has a variable effect on plasma cholinesterase activity.

In conclusion, patients with liver failure exhibited markedly reduced plasma clearance and a longer elimination half-life for mivacurium. The duration of block was approximately 1.5 times normal in patients with kidney disease and approximately 3 times normal in those with liver failure.

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THIOPENTONE AND ETOMIDATE CONCENTRATIONS IN MATERNAL AND UMBILICAL PLASMA, AND IN COLOSTRUM

Z. ESENER, B. SARIHASAN, H. GÜVEN AND E. ÜSTÜN

SUMMARY

We have measured concentrations of etomidate and thiopentone in maternal plasma, umbilical venous plasma and colostrum after induction of anaesthesia in 40 patients undergoing Caesarean section. Mean plasma etomidate concentration declined rapidly (1242.0 ng ml^{-1} at 5 min, 434.0 ng ml^{-1} at 15 min, 64.2 ng ml^{-1} at 30 min, 7.0 ng ml^{-1} at 60 min and undetectable 2 h after the injection). Mean plasma concentrations of thiopentone declined more slowly (6.09 μg ml^{-1} at 5 min, 2.64 μg ml^{-1} at 2 h, 1.35 μg ml^{-1} at 4 h, 0.86 μg ml^{-1} at 9 h and 0.59 μg ml^{-1} at 12 h). Mean umbilical venous thiopentone concentration was 4.72 μg ml^{-1}, whereas the thiopentone concentration in the maternal sample at 5 min was 6.09 μg ml^{-1}, giving an umbilical:maternal vein ratio of 1:1.3. Mean umbilical etomidate concentration was 51.7 ng ml^{-1} and the corresponding maternal vein sample (5 min) was 1242.0 ng ml^{-1} ($P < 0.001$), giving an umbilical:maternal vein ratio of 1:24. Mean concentrations of thiopentone in colostrum were 1.98 μg ml^{-1} at 30 min, 0.91 μg ml^{-1} at 4 h and 0.59 μg ml^{-1} at 9 h, colostrum:plasma ratios at 4 h and 9 h being 0.67 and 0.68, respectively. Mean concentrations of etomidate in colostrum were 79.3 ng ml^{-1} at 30 min and 16.3 ng ml^{-1} at 2 h, being undetectable at 4 h. The colostrum:plasma etomidate concentration ratio was 1.2 at 30 min. We conclude that, although plasma and colostrum concentrations of thiopentone and etomidate declined rapidly, the decrease was faster with etomidate. (Br. J. Anaesth. 1992; **69**: 586–588)

KEY WORDS

Anaesthetics, intravenous: thiopentone, etomidate. Anaesthesia: obstetric. Pharmacokinetics: plasma, umbilical vein cord and colostrum concentrations.

Thiopentone is used extensively for induction of anaesthesia in obstetrics [1]. However, barbiturates cause cardiorespiratory depression. There is abundant evidence that thiopentone crosses the placenta easily and is found in significant concentrations in umbilical cord blood. Etomidate is associated with little or no cardiovascular or respiratory effects [2–4] and the clinical status of the newborn after Caesarean section has been shown to be satisfactory [3, 5–7].

In some departments it is common practice to discard the first portions of milk after general anaesthesia, to avoid any side effects of the anaesthetic agents. Reports of the excretion of etomidate in colostrum after induction of anaesthesia have, to our knowledge, not been published.

The aim of this study was to determine the postanaesthetic concentrations of thiopentone and etomidate in maternal and neonatal plasma, and in colostrum after induction doses of thiopentone and etomidate.

PATIENTS AND METHODS

We studied 40 healthy pregnant women at term undergoing Caesarean section. Each patient received a single i.v. injection of either thiopentone 5 mg kg^{-1} ($n = 20$) or etomidate 0.3 mg kg^{-1} ($n = 20$) for induction of anaesthesia.

Patients were premedicated with atropine 0.5 mg i.m. or 0.25 mg i.v. Left lateral tilt was used and the lungs were preoxygenated for 3–4 min. After thiopentone or etomidate, suxamethonium 1.5 mg kg^{-1} was given and the trachea was intubated, using cricoid pressure. Anaesthesia was maintained with 50% nitrous oxide in oxygen with halothane not exceeding 0.5%, until delivery of the infant. After delivery the nitrous oxide concentration was increased to 66% and halothane was increased as needed. Neuromuscular block was maintained with additional increments of suxamethonium.

The end of the injection of thiopentone or etomidate was taken as the starting point for obtaining blood samples.

In the thiopentone group, maternal blood samples were obtained at 5 min, 2, 4, 9 and 12 h, and colostrum samples at 30 min, 4 and 9 h after induction.

In the etomidate group, maternal blood samples were obtained at 5, 15, 30 and 60 min and 2 h, and colostrum samples at 30 min, 2 and 4 h after induction.

Umbilical cord blood (umbilical vein) was obtained immediately after delivery.

Plasma was separated immediately and samples for thiopentone were stored at −18 °C. Samples

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TABLE I. *Patient characteristics (mean (range or* SEM*)): age, weight, gestational age and induction to delivery (I–D) interval in the thiopentone and etomidate groups*

Group	Age (yr)	Weight (kg)	Gestational age (weeks)	I–D interval (min)
Thiopentone	28.3 (22–38)	75 (2)	39.9 (0.6)	7.3 (2.1)
Etomidate	28.2 (19–41)	74 (2)	40.1 (0.7)	7.0 (0.9)

were thawed at room temperature before the extraction process. Thiopentone was extracted from plasma and colostrum with n-hexane containing 1.5% iso-amyl alcohol and re-extracted into sodium hydroxide 2.5 mol litre^{-1} [8]. Thiopentone concentrations were measured using a spectrophotometric method (SIM AMINCO SMF 500) with absorbance at 305–505 µm [9].

To each 1-ml aliquot of plasma for etomidate measurement, heparin 0.002 g and potassium fluoride 10 µl (to inhibit esterase activity) were added and stored at −18 °C. After the samples were thawed and etomidate extracted from plasma or colostrum (with pentane, by mixing on a vortex mixer and discarding the upper layer twice), spectrophotometric (VARIAN DMS 100) measurement of etomidate was carried out using the absorbance at 235 µm.

Colostrum samples also were stored at −18 °C until analysis.

Results are given as mean (SEM). Student's *t* test was used for statistical analysis of the data within each group.

RESULTS

The two groups were similar in mean age, weight, gestational age and induction–delivery (I–D) interval (table I).

Thiopentone group. Maternal concentrations of thiopentone at 5 min (sample closest to delivery) were in the range 4–12.1 µg ml^{-1} (mean 6.09 (SEM 0.4) µg ml^{-1}). Mean maternal plasma concentration was 2.64 (0.3) µg ml^{-1} (range 0.8–7.0 µg ml^{-1}) at 2 h, 1.35 (0.2) µg ml^{-1} (range 0.1–3.7 µg ml^{-1}) at 4 h, 0.86 (0.1) µg ml^{-1} (range 0.4–1.4 µg ml^{-1}) at 9 h and 0.59 (0.1) µg ml^{-1} (range 0.2–1.2 µg ml^{-1}) at 12 h.

In the umbilical vein, thiopentone concentrations ranged from 2.3 to 10.2 µg ml^{-1} (mean 4.72 (0.4) µg ml^{-1}).

Mean concentrations of thiopentone in colostrum at 30 min, 4 h and 9 h after the injection were 1.98 (0.2) µg ml^{-1} (range 0.6–4.7 µg ml^{-1}), 0.91 (0.1) µg ml^{-1} (range 0.4–1.9 µg ml^{-1}) and 0.59 (0.1) µg ml^{-1} (range 0.3–1.4 µg ml^{-1}), respectively.

Etomidate group. Maternal concentrations of etomidate at 5 min (sample closest to delivery) were in the range 340–2500 ng ml^{-1} (mean 1242.0 (SEM 146) ng ml^{-1}). Mean maternal plasma concentrations at 5 min, 15 min, 30 min and 1 h after the injection of etomidate were 434.0 (82) ng ml^{-1} (range 0–1400 ng ml^{-1}), 64.2 (10) ng ml^{-1} (range 0–145 ng ml^{-1}), 7.0 (2.6) ng ml^{-1} (range 0–35 ng ml^{-1}) and 0.5 (0.1) ng ml^{-1} (range 0.2–1.2 ng ml^{-1}), respectively. There was no detectable etomidate in any of the 2-h samples.

In the umbilical vein, etomidate concentrations were in the range 0–190 ng ml^{-1} (mean 51.7 (10.3) ng ml^{-1}).

Mean concentrations of etomidate in colostrum at 30 min and 2 h after the injection were 79.3 (21.5) ng ml^{-1} (range 0–420 ng ml^{-1}) and 16.2 (4.1) ng ml^{-1} (range 0–60 ng ml^{-1}), respectively. No etomidate could be detected in any of the 4-h samples.

DISCUSSION

Although the measurement of plasma etomidate concentrations can be carried out accurately by several methods including gas chromatography (GC) [10–13], gas–liquid chromatography (GLC) [14] or high performance liquid chromatography (HPLC) [15], GC and GLC require considerably longer and are more laborious than HPLC [13]. We used an extraction method described for HPLC by Ellis and Beck [15] and u.v. spectrophotometry [16] based, like HPLC, on ultraviolet detection for estimation of the substrate. It was therefore possible to complete the extraction and estimation process in 1–1.5 h.

Etomidate is metabolized largely by esteratic breakdown [9, 17]. Continuing esteratic activity causes a decrease in etomidate concentration in blood samples also [18]. Therefore saturated potassium fluoride 10 µl was added to 10 ml of blood as a preservative.

We found that plasma etomidate concentrations declined rapidly. Doenicke and colleagues [11] found a plasma etomidate concentration at 30 min similar to our data. In Gregory and Davidson's study [7], in contrast, maternal etomidate concentrations at delivery were found to be smaller than the present data. This could be attributable to the greater I–D interval in their study.

Plasma thiopentone concentration decreased more slowly than etomidate concentration. Brodie and colleagues [19] reported that thiopentone concentrations decreased rapidly for the first 30 min then more slowly, with mean concentrations similar to those in our study. Andersen and colleagues [20] reported also that thiopentone was detected in plasma for up to 36 h. Although we did not obtain 36 h samples, thiopentone was detected in all the samples at 12 h (approximately 10% of the mean concentration at 5 min).

Thiopentone crosses the placental barrier readily, fetal and maternal concentrations equilibrating within 2–3 min [21, 22]. We did not obtain fetal blood in this study, but the umbilical plasma concentration of thiopentone in the blood sample obtained immediately after the cord had been clamped (mean 7.3 (2.1) min after the injection of thiopentone) was 4.72 (0.4) µg ml^{-1}. Mean concentration in the closest maternal sample (5 min) was 6.09 (0.4) $\mu g\ ml^{-1}$, giving an umbilical : maternal ratio of 1:1.3. Data on umbilical concentrations of thiopentone were in agreement with those of Finster and colleagues [23] and Flowers and Hill [21].

We found an umbilical : maternal venous etomidate concentration ratio of 1:24; Gregory and Davidson [7] reported this ratio as 1:2. This difference may be explained by the differences in doses of etomidate (0.4 $mg\ kg^{-1}$ *vs* 0.3 $mg\ kg^{-1}$), I–D intervals (15.2 min *vs* 7.0 min) and the fact that, in our study, umbilical samples were taken later than maternal samples (7.0 min *vs* 5 min).

Drugs present in maternal circulation reach the mammary gland and milk by passive diffusion through glandular epithelium [20]. Colostrum : plasma ratios of thiopentone at 4 h and 9 h were 0.67 and 0.68, respectively. Andersen and colleagues [20] also found this ratio to be less than 1. The colostrum : plasma etomidate ratio was 1.2 at 30 min. While no etomidate could be detected in any of the 2-h plasma samples, etomidate was still detectable in nine of 20 colostrum samples, with a mean value of 16.2 (4) $ng\ ml^{-1}$ at 2 h. Rapid decline in etomidate concentrations in colostrum may be an advantage in early feeding of the newborn after Caesarean section.

In conclusion, our results indicate that, although plasma concentrations of thiopentone and etomidate declined rapidly, this decrease was faster for etomidate.

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SPINAL ANAESTHESIA FOR CAESAREAN SECTION: COMPARISON OF 22-GAUGE AND 25-GAUGE WHITACRE NEEDLES WITH 26-GAUGE QUINCKE NEEDLES

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SUMMARY

We have studied 150 women undergoing elective Caesarean section under spinal anaesthesia. They were allocated randomly to have a 22-gauge Whitacre, a 25-gauge Whitacre or a 26-gauge Quincke needle inserted into the lumbar subarachnoid space. The groups were compared for ease of insertion, number of attempted needle insertions before identification of cerebrospinal fluid, quality of subsequent analgesia and incidence of postoperative complications. There were differences between groups, but they did not reach statistical significance. Postdural puncture headache (PDPH) was experienced by one mother in the 22-gauge Whitacre group, none in the 25-gauge Whitacre group and five in the 26-gauge Quincke group. Five of the six PDPH occurred after a single successful needle insertion. Seven of the 15 mothers in whom more than two needle insertions were made experienced backache, compared with 12 of the 129 receiving two or less ($P < 0.001$*). We conclude that the use of 22- and 25-gauge Whitacre needles in elective Caesarean section patients is associated with a low incidence of PDPH and that postoperative backache is more likely when more than two attempts are made to insert a spinal needle.* (Br. J. Anaesth. 1992; **69**: 589–594)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: spinal. Complications: headache, backache. Equipment: spinal needles.

The resurgence of interest in spinal (subarachnoid) anaesthesia, particularly for lower segment Caesarean section, has been accompanied by refinements in spinal needles. There has been a trend towards the production of very small gauge needles and renewed interest in needles with a conical or pencil point (Whitacre [1], Sprotte [2]) which separate rather than cut dural fibres. Smaller gauge and pencil point needles are designed to reduce the most distressing complication of spinal anaesthesia, namely postdural puncture headache (PDPH). The incidence of such headaches is greatest in obstetric patients [3, 4].

Recent *in vitro* studies comparing the rate of transdural leak of fluid have shown that 22-gauge Whitacre needles caused significantly less leak than 22-gauge Quincke (cutting bevel) needles, and that leakage rate varied directly with the size of Quincke needles between 22- and 29-gauge [5, 6]. However, in a study of 29-gauge needles [7], cerebrospinal fluid (CSF) was not detected, and therefore anaesthesia was not possible, in 8% of patients. Failure to confirm dural puncture has occurred also with 25-gauge spinal needles [8]. Furthermore, there is a belief among devotees of regional anaesthesia that slow flowback of CSF through 25- and 26-gauge needles may, particularly in inexperienced hands, lead to repeated unrecognized dural puncture and that this may contribute to PDPH.

The spinal needle in common use at our maternity hospitals has been a 26-gauge Quincke needle. The marketing of a 22-gauge Whitacre needle gave us the opportunity to compare these two needles and in particular to assess the effect of the number of needle insertions on the postoperative complication rate. Just before the study was commenced, a 25-gauge Whitacre needle became available and this was included in the study.

PATIENTS AND METHODS

This was a collaborative study between the maternity units at St Michael's Hospital, Bristol and St Mary's Hospital, Portsmouth. The approval of the local Ethics Committees at the two hospitals was gained to study a total of 150 women of ASA grade I undergoing spinal anaesthesia for elective Caesarean section. Each woman was allocated by random number selection to one of three different spinal needle groups. Dural puncture was attempted with a 22-gauge Whitacre needle in 50 mothers, with a 25-gauge Whitacre needle in another 50 and a 26-gauge Quincke needle in 50 mothers. Anaesthetists of all grades with previous experience of this technique performed the blocks.

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Fifteen minutes before attempted insertion of the spinal needle, a prophylactic i.m. injection of ephedrine 15 mg was given, an i.v. cannula was inserted and Hartmann's solution 1 litre was infused. The mothers lay in the left lateral decubitus position and the lumbar 3–4 interspace was identified. A midline puncture at 90° to the skin and with the needle bevel/orifice pointing laterally was performed under aseptic conditions. Twenty-five- and 26-gauge needles were inserted through an introducer.

Identification of a free flow of CSF marked the endpoint of needle placement. To allow for a slow return of CSF, operators were asked to wait for up to 1 min and then if no CSF had appeared, to make an additional check by aspirating the needle with a syringe. If aspiration was negative, the needle was withdrawn and a second attempt made. Any backward movement of the needle followed by redirection was classified as a further attempt.

After identification of CSF, 0.5% bupivacaine in 8% glucose 2–2.5 ml was injected through the spinal needle over 15 s. After withdrawal of the needle, the patient was turned to the left wedged lateral position, the position in which the operation was performed.

A record was kept for each patient of the number of atempts at dural puncture. A second anaesthetist, who had no knowledge of the spinal needle used or the number of attempted needle insertions, tested the adequacy of the spinal block. He recorded the block height, missed segments and motor effects (Bromage scale) at 2 and 5 min, and thereafter at 5-min intervals until analgesia adequate for surgery was obtained. The ECG was monitored continuously and indirect measurements of arterial pressure were made by Dinamap at 5-min intervals.

After operation, mothers were nursed in a semi-recumbent supine position with a bed cradle over the legs until sensation returned. They were allowed to mobilize as they wished when sensation and motor function had returned. Additional analgesia was available as i.m. opioid or oral soluble paracetamol.

Twenty-four hours after dural puncture, each patient was asked to complete a standard questionnaire on the return of sensory and motor function, bladder function and the presence or absence of headache, backache and other complications. At 24 h also, the second "blind" anaesthetist visited the patient. His duty was to check that the questionnaire had been completed and to record the patient's temperature. If a headache had been reported, he completed a second questionnaire ascertaining the onset and distribution of the headache, the effect of posture and if there was any visual or auditory disturbance. A headache was categorized as a postdural puncture headache (PDPH) if it was worse on sitting or standing and relieved or reduced by lying flat. Otherwise, the headache was recorded as a non-postdural puncture headache (NPDPH). The headache was graded [9] as mild (not interferring with activity, facial make-up applied, able to care for child); moderate (able to care for child, ambulation for short period, little interest in appearance); severe (unable to care for child, up only to toilet if at all, tinnitus or diplopia).

The regimen for treatment of headache was adjusted to each patient's response and allowed a progression from simple analgesics and increased oral fluids to i.v. caffeine [10] and extradural blood patch.

The second anaesthetist visited all patients again at 72 h. Visits at 48 h or beyond 72 h were made only if there were symptoms at 24 h or a request for a further visit was made by the ward staff.

The study groups were compared for the number of attempts required to achieve dural puncture, the adequacy of spinal block and the incidence of headache and other postoperative complications. The effect of the number of needle insertions on the incidence of postoperative headache and backache was also studied. For analysis of data, chi-square with Yates' correction was used, and Fisher's exact test where group numbers were very small. $P < 0.05$ was taken as statistically significant.

RESULTS

There was no difference between the three groups in age, weight or height (table I). There was no difference also between the groups in the general characteristics of the spinal blocks: volume of local anaesthetic used, height of block, pre-block and smallest systolic arterial pressure (table II).

There were 49 successful dural punctures with the 22-gauge Whitacre needle, 47 with the 25-gauge variety and 48 with the 26-gauge Quincke point needle (table III). The number of needle insertions necessary before cerebrospinal fluid was obtained was not significantly different between the groups. Six patients were withdrawn from the study because of a failure to identify the subarachnoid space with the trial needle. Successful dural punctures were achieved with an alternative spinal needle in one patient from the 25-gauge Whitacre group and one patient in the 26-gauge Quincke group. Analgesia in another patient from the 25-gauge Whitacre group was produced via the extradural route; one patient in each group received a general anaesthetic.

The quality of spinal anaesthesia was satisfactory in 46 patients (93.9%), 41 patients (87.2%) and 42

TABLE I. *Patient characteristic (mean (range or SD))*

	22-gauge Whitacre	25-gauge Whitacre	26-gauge Quincke
Age (yr)	29.9 (16–45)	28.8 (19–39)	28.8 (16–42)
Weight (kg)	62.7 (11.1)	63.9 (11.2)	61.5 (11.0)
Height (m)	1.62 (0.08)	1.62 (0.07)	1.61 (0.07)

TABLE II. *Characteristics of spinal block (mean (SD))*

	22-gauge Whitacre	25-gauge Whitacre	26-gauge Quincke
Local anaesthetic			
Volume (ml)	2.24 (0.2)	2.2 (0.2)	2.2 (0.2)
Height of block			
Right	T3.3 (1.75)	T3.6 (1.4)	T3.3 (1.6)
Left	T3.3 (1.0)	T3.74 (1.4)	T3.2 (1.5)
SAP (mm Hg)			
Before block	130 (13)	128 (17)	128 (13)
Smallest value	108 (11)	105 (15)	106 (13)

TABLE III. *Successful dural puncture compared with number of attempted needle insertions*

Number of attempts	22-gauge Whitacre	25-gauge Whitacre	26-gauge Quincke
1	39	32	34
2	4	12	8
>2	6	3	6
Totals	49	47	48

TABLE IV. *Quality of spinal anaesthesia*

	22-gauge Whitacre	25-gauge Whitacre	26-gauge Quincke
n	49	47	48
Adequate analgesia	46	41	42
Missed segments	0	4	1
Peritoneal discomfort	2	1	5
Shoulder tip pain	1	1	1

TABLE V. *Postoperative problems. PDPH = Postdural puncture headache; NPDPH = Non-postdural puncture headache*

	22-gauge Whitacre	25-gauge Whitacre	26-gauge Quincke
n	49	47	48
Headache			
PDPH	1	0	5
NPDPH	1	0	1
Backache	11	4	4
Dysuria	0	1	1

TABLE VI. *Headaches. PDPH = Postdural puncture headache; NPDPH = Non-postdural puncture headache; W = Whitacre; Q = Quincke. Onset = Time after spinal puncture*

Headache	Patient No.	Size of needle	Number of insertion attempts	Onset (h)	Severity
PDPH	111	22-gauge W	1	36	Moderate
	9	26-gauge Q	4	40	Severe
	26	26-gauge Q	1	18	Severe
	57	26-gauge Q	1	57	Moderate
	109	26-gauge Q	1	23	Severe
	144	26-gauge Q	1	26	Moderate
NPDPH	127	22-gauge W	4	13	Mild
	22	26-gauge Q	1	<24	Mild

TABLE VII. *Incidence of postoperative backache compared with number of attempted needle insertions (all needles).* $\chi^2 = 16.629$*; 2 degrees of freedom. *** Significant difference (P < 0.001) between groups relates to the incidence of backache associated with more than two attempted needle insertions*

No. of attempts	No. of patients	Number with Backache	Number with No backache	χ^2 Backache	χ^2 No backache
1	105	9	96	1.698	0.258
2	24	3	21	0.009	0.007
>2	15	7	8	12.727	1.936
Totals	144	19 ***	127	14.434	2.195

patients (87.5%) in the 22-gauge Whitacre, 25-gauge Whitacre and 26-gauge Quincke groups, respectively (table IV). Patient dissatisfaction was expressed in terms of missed segments of analgesia, peritoneal discomfort at the time of surgical closure of the wound and shoulder tip pain, but the number of complainants was small and differences between groups were not significant.

The incidence of postoperative complications is recorded in table V. PDPH occurred in six patients: five followed the use of 26-gauge Quincke needles and one followed a 22-gauge Whitacre dural puncture. There were no headaches in the women in whom a 25-gauge Whitacre needle had been used. The difference in PDPH between groups was not statistically significant.

Further details of the headaches are shown in table VI. A single successful needle insertion was associated with five of the six PDPH. Onset of headache was from 18 to 57 h after dural puncture. Headaches were classified as severe or moderate, but an extradural blood patch was administered to only one patient. The remainder were alleviated successfully with simple analgesics, oral fluids and on two occasions i.v. caffeine 500 mg. Four mothers with PDPH had mild neck stiffness, two were photophobic and one complained of transient unilateral deafness. The two NPDPH were mild and occurred on the first day after operation. No headache was accompanied by a pyrexia.

Postoperative backache was most prevalent in the group of women in whom a 22-gauge Whitacre needle had been used, but the number of cases was not significantly different from that in the two other groups (table V). Additional analysis of the number of attempted needle insertions for all needles, with the number of patients reporting or not reporting backache, revealed a significant difference ($P < 0.001$) which was attributable entirely to the number of patients reporting backache after more than two attempted needle insertions (table VII).

Two mothers experienced postoperative dysuria and one required short-term catheterization (table V). In neither was the dysuria associated with pyrexia or complaint of backache.

DISCUSSION

Ease of needle insertion

There are few studies [8, 11] which examine the technical difficulties involved in the use of different spinal needles. The needles compared in this study were inserted predominantly by trainees of varying experience at two maternity hospitals. All had previous experience of spinal anaesthesia, but few had experience of pencil point needles.

The 22-gauge Whitacre needle was associated with the greatest incidence of successful dural puncture following a single needle insertion (78%) and the smallest failure rate (2%). The 25-gauge

Whitacre needle, in contrast, was the least likely to succeed initially (64%) and was associated also with the greatest failure rate (6%). However, the 25-gauge Whitacre needle was marginally the most successful locator of the subarachnoid space within two attempted needle insertions. None of these differences between groups was statistically significant.

The most frequently recorded comment with all three needles in relation to two or more attempts to puncture the dura was that there was no feeling as to what depth the needle had reached until CSF began to flow. Occasionally, particularly with the Whitacre needle, the comment "tough ligaments" was made. A few recorded a distinctive click on dural puncture with the cutting bevel needle, which was not always apparent with the pencil point needles.

The authors formed the impression that the combination of smaller gauge and unfamiliarity with the needle was responsible for the marginal third place of the 25-gauge Whitacre needle in respect of failure to identify CSF. As with any practical skill, the acquisition of a new technique rarely occurs immediately [12].

Adequacy of analgesia

Adequate analgesia without the need for further supplementation was achieved in the majority of spinal anaesthetics. The 22-gauge Whitacre needle was most successful in this regard. Those mothers with discomfort usually had unilateral segments of inadequate analgesia or discomfort of the peritoneum at the time of surgical closure. There were no significant differences in the distribution of these complaints between needle groups, although missed segments were most frequent with the 25-gauge Whitacre needle, and peritoneal discomfort with the 26-gauge Quincke needle (table IV).

Hyperbaric 0.5% bupivacaine in 8% glucose was chosen for this study for its ability to extend to thoracic segments [13]. A level of sensory anaesthesia above T6 is necessary for Caesarean section. A volume range of bupivacaine 2–2.5 ml was chosen to allow reduced dosage in women of short stature. In those women with inadequate analgesia, there was no correlation with the dose of local anaesthetic used.

The number of studies in which hyperbaric bupivacaine has been used as a spinal anaesthetic for Caesarean section is not large. A study in which 20 patients received 2.5 ml through a 26-gauge needle reported a wide range of block duration and the earliest onset of postoperative pain 50 min after dural puncture [14]. Smaller doses (1.5–2 ml) have been used, in combination with a head-down tilt, to produce reliable initial somatic sensory block, although i.v. pethidine supplementation was almost always necessary after delivery, during peritoneal manipulation and uterine traction [15]. Russell and Holmqvist chose a volume of 2.5 ml and achieved adequate analgesia in all patients [16]. In our study, hyperbaric bupivacaine was deposited in the subarachnoid space with the mothers lying in a left lateral position and after this they were rolled to a left wedged lateral position. Other workers have reported that, by injecting the local anaesthetic in the right lateral position and immediately turning the patient to the left wedged lateral position, adequate analgesia is guaranteed [16, 17].

A non-obstetric study of 22-gauge Whitacre needles showed a higher sensory level of spread when the needle was inserted with the orifice pointing cephalad rather than caudad [18]. There was no mention of inadequate analgesia, but a wide range of both level and duration of spinal block was reported. A non-controlled series of spinal anaesthesia for Caesarean section in which a 20-gauge Whitacre needle was used also stressed the importance of directing the opening of the needle cephalad to achieve an adequate height of block [19].

Headaches

It has been known since the 1950s that headaches after dural puncture are more frequent in obstetric patients [3, 4]. The proposal that a cone tipped needle would reduce the incidence of PDPH predates this by 30 years [20]. In a non-controlled series of obstetric patients, published in 1960, there was a PDPH incidence of 0.63% (two mild headaches) following the use of 22-gauge pencil point needles [21].

A zero incidence of headache, as occurred after the use of the 25-gauge Whitacre needle in our study, was found also for the 24-gauge Sprotte needle in a similar controlled study in obstetric patients [22]. The Sprotte needle was compared to a 25-gauge cutting bevel needle, the use of which was associated with a 14.5% incidence (eight patients) of PDPH [22]. Other controlled studies in obstetric patients have appeared as abstracts and reported headache frequencies of 4% (one patient) with a 22-gauge Whitacre needle against 25% (six patients) with a 26-gauge Quincke needle [23] and 3.6% (two patients) with a 24-gauge Sprotte needle compared with 1.75% (one patient) with a 22-gauge Sprotte needle [24].

In this study, the incidence of PDPH in the group of mothers in whom the 26-gauge Quincke needle had been used was 10.4%. This was not significantly different from the low incidence in the other needle groups. However, with the supporting evidence of the other studies quoted, the balance of favour is against the use of 26-gauge cutting bevel needles in obstetric patients.

The belief that repeated unrecognized dural punctures may cause an increased incidence of PDPH has not been supported by this study.

PDPH were assessed objectively as moderate or severe depending on the degree of compromised activity they imposed on the mother [9]. No mother complained of diplopia or tinnitus. The time of headache onset varied between 18 and 57 h. In addition, there were two other headaches (NPDPH) which were mild, began less than 24 h after dural puncture and subsided without treatment. It has recently been postulated in a prospective, non-ramdomized study of 2511 spinal blocks for Caesarean section [25] that the CSF leak component of PDPH is not seen before 24–36 h and that there is an early (<36 h) phase which relates to the type and baricity of local anaesthetic used. Hyperbaric glucose-containing amide local anaesthetics were more often associated with early phase headaches than were isobaric esters. Two suggestions were made for the aetiology of this early phase effect. First, residual local anaesthetic could cause intracranial vasoconstriction and this may explain the effectiveness of caffeine [10] and non-steroidal anti-inflammatory drugs. The second suggestion was that the effect is caused by the large concentration of glucose acting as an osmotic agent or an irritant.

In this study, PDPH were treated progressively with simple analgesics and increased oral fluids and, in the latter phases of the study, three mothers (Nos 109, 111 and 114 (table VI)) were treated with i.v. caffeine according to the regimen of Jarvis, Greenawalt and Fagraeus [10]. These workers infused caffeine sodium benzoate 500 mg in 1 litre of i.v. fluid over 1 h, followed by a further 1 litre of fluid without added drug over 2 h in 18 patients experiencing PDPH. If one completed treatment did not adequately relieve the headache, after a further 4 h a second identical course of treatment was allowed. With this regimen, 14 of the 18 patients were successfully relieved of their headache. In our study, a single treatment alleviated the headaches of patients Nos 111 and 114. The headache of patient No. 109 was undiminished by two courses of treatment and was finally relieved by an extradural blood patch 48 h after dural puncture.

Backache

A retrospective study of an obstetric population reported that use of extradural anaesthesia for elective Caesarean section was no more likely than general anaesthesia to lead to a complaint of backache of more than 6 weeks duration [26]. Extradural anaesthesia for labour was a different matter, and a significantly greater incidence of long term backache in this group was attributed to the stressed postures which effective analgesia and muscle relaxation may allow. Early postoperative rather than long-term pain in the lower back is the most frequently reported complaint after spinal anaesthesia, and frequencies as great as 55% in a study of outpatients [27] and 26% after the use of a 29-gauge needle [11] have been reported. The incidence of postoperative backache in this study was 22.4%, 8.5% and 8.3% with the 22- and 25-gauge Whitacre and the Quincke needles, respectively. The differences were not significant between groups. No complaint of backache was deemed sufficiently severe to be followed beyond 72 h. We are not aware of studies investigating the incidence of long-term backache after spinal anaesthesia.

In this study, the increased incidence of backache in the 22-gauge needle group compared with the two other groups is of interest. Of the 11 mothers who reported backache after the use of a 22-gauge Whitacre needle, seven were in the sub-group of 39 who had had a single successful needle insertion and the remaining four were among the six in whom more than two attempted needle insertions were made (table III). There was no significant difference between needle groups in the subgroups.

The finding that a significantly greater incidence of early postpartum backache was associated with repeated insertions of spinal needles was not surprising and was related presumably to soft tissue or periosteal trauma by the needles.

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EFFECT OF FENTANYL ON VENTILATORY RESISTANCES DURING BARBITURATE GENERAL ANAESTHESIA

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SUMMARY

*Fentanyl has been shown to increase the overall resistance to inspiratory flow of the ventilatory system (*Rmax*).* Rmax *is the sum of the airway resistance (*Raw*) and of the non-Newtonian resistance (*ΔR*) which may result from the viscoelastic properties of the thoracic tissues, from inequalities of the regional time constants within the lung, or from both. A bronchoconstrictor challenge may increase the magnitude of variation in regional time constants. Thus, in order to describe the effect of fentanyl on the two components of* Rmax*, this study was performed, with the end-inflation occlusion method, during paralysis and mechanical ventilation in 10 normal men undergoing barbiturate anaesthesia for minor urological procedures. The patients were anaesthetized with methohexitone and paralysed with vecuronium. Before administration of fentanyl,* ΔR *accounted for 56% of* Rmax*. Fentanyl* $5\ \mu g\ kg^{-1}$ *elicited a significant increase in* Rmax *(+34.5%;* $P = 0.005$*) and a parallel increase in both* Raw *(+35.2%,* $P = 0.017$*) and* ΔR *(+33.5%,* $P = 0.005$*). The increase in* Raw*, but not in* ΔR*, was reversed by atropine, suggesting that the increase in these two components of* Rmax *was not linked. Thus fentanyl increased both components of* Rmax*, but the effects of fentanyl on* Raw *and* ΔR *seemed to depend on different mechanisms.* (Br. J. Anaesth. 1992; **69**: 595–598)

KEY WORDS

Anaesthesia: general. Analgesics: fentanyl. Lung: respiratory resistance.

Fentanyl increases ventilatory impedance in man. The drug induces truncal muscular rigidity [1] and bronchoconstriction [2] and it increases the overall resistance to inspiratory flow of the ventilatory system (*R*max) [3]. This resistance is the sum of two distinct resistances [4]: airway resistance (*R*aw) and non-Newtonian resistance (ΔR) which varies with the ventilatory pattern [5]. ΔR may result from either or both of two distinct phenomena [6, 7]—viscoelasticity of the thoracopulmonary tissues or inhomogeneity of regional time constants within the lungs; the latter is considered to be negligible in the normal subject. However, a bronchoconstrictor challenge may induce or aggravate this phenomenon [8].

The aim of this study was to describe the effects of fentanyl on *R*max and on its two components, ΔR and *R*aw, in anaesthetized, paralysed man undergoing mechanical ventilation. For this purpose we used the end-inflation occlusion method [7]. The study was completed with the description of the effect of fentanyl on the elastic properties of the ventilatory system: static elastance (*E*st) and dynamic elastance (*E*dyn). Moreover, as atropine decreases *R*max during general anaesthesia in man [9], its effects on the fentanyl-induced modifications of the ventilatory mechanics were also described.

PATIENTS AND METHODS

After approval from the local Ethics Committee, we studied 10 men undergoing elective surgery for testicular biopsy under general anaesthesia (mean age 30 yr (range 26–34 yr) weights 69.7 (SD 5.9) kg). The exclusion criteria were clinical or radiological abnormality of the ventilatory system; heavy smoking; suspected (history of atopy) or overt (history of wheezes) bronchial hypersensitivity; treatment with a beta blocker [10].

Mechanical ventilation was performed with a Servo Ventilator 900 D (Siemens–Elema, Sweden). This ventilator produces a constant inflation flow ($\dot{V}$I), and an accurate tidal volume (*V*T) [11, 12]. It allows end-expiratory and end-inspiratory airway occlusions [13]. The ventilatory circuit comprised short tubing (40 cm) without a humidifier, in order to reduce the compressible volume. Each disposable tracheal tube (internal diameter 8 mm) was fitted with a lateral port at its distal end ("Blue Line", ref. 100/196/080 Portex Great Britain), that allowed measurement of the tracheal pressure [14]. The port was connected to a pressure transducer (model SK ± 20 cm H_2O, EFFA, Le Pré St Gervais, France) and a linear amplifier (MRC 4411, LEIM, Aix en Provence, France). The pressure signal and the flow signal fed by the ventilator were recorded on a Gould TA 550 polygraph, at a paper speed of 15 mm s^{-1}.

Ventilatory mechanics were studied using the end-inspiratory occlusion method which has already been

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TABLE I. *Overall resistance of the ventilatory system* (Rmax), *airway resistance* (Raw), *non-Newtonian resistance* (ΔR) *and contribution of* ΔR *to* Rmax (ΔR/Rmax) (*mean* (SD)) *at baseline* (T_0), *6 min after fentanyl 5 µg* kg^{-1} (T_1) *and 6 min after fentanyl 1.75 µg* kg^{-1} (T_2). † *Friedman test*

	Resistance (cm H_2O litre^{-1} s)			
	T_0	T_1	T_2	*P*†
*R*max	3.62 (0.87)	4.87 (1.2)	3.95 (0.99)	0.0002
*R*aw	1.59 (0.47)	2.15 (0.8)	1.40 (0.55)	0.02
ΔR	2.03 (0.56)	2.71 (0.5)	2.54 (0.59)	0.0002
ΔR/*R*max (%)	56 (0.076)	56.8 (0.075)	64.9 (0.071)	0.02

TABLE II. *Dynamic elastance* (Edyn) *and static elastance* (Est) *of the ventilatory system* (*mean* (SD)) *at baseline* (T_0), *6 min after fentanyl 5 µg* kg^{-1} (T_1) *and 6 min after fentanyl 1.75 µg* kg^{-1} (T_2). † *Friedman test*

	Elastance (cm H_2O litre^{-1})			
	T_0	T_1	T_2	*P*†
*E*dyn	14.30 (2.6)	15.21 (2.67)	15.07 (2.63)	0.0001
*E*st	12.27 (2.36)	12.50 (2.41)	12.53 (2.41)	0.18

described extensively [7]. Briefly, at the end of the inflation of a preset tidal volume (*V*T), an occlusion of about 6 s was performed at the ventilator valves (while pressing the "inspiratory hold" button) to detect any air leak. After airway occlusion, there was an abrupt decrease in tracheal pressure from a maximum pressure *P*max to an inflection point P_1, and a more gradual decay to a plateau pressure which is the elastic recoil pressure of the ventilatory system (*P*el) [12]. Gas exchange during occlusion has a negligible effect on *P*el [15], which was measured after 3 s of the end-inspiratory occlusion. The initial decrease in pressure ($P\text{max}-P_1$) reflects the resistive pressure attributable to the airway resistance (*R*aw) during the constant inflation flow preceding occlusion ($\dot{V}\text{I}$). Thus *R*aw equals ($P\text{max}-P_1$) $\dot{V}\text{I}^{-1}$. Similarly, overall resistance, *R*max, was calculated as $R\text{max} = (P\text{max}-P\text{el})\ \dot{V}\text{I}^{-1}$; additional resistance (ΔR) = $R\text{max}-R\text{aw}$; static elastance (*E*st) = *P*el $V\text{T}^{-1}$ [12]; dynamic elastance (*E*dyn) = *P*max $V\text{T}^{-1}$. The possibility of an intrinsic PEEP (PEEPi) was excluded by an end-expiratory occlusion performed at the ventilator valves (while pressing the "expiratory hold" button). It would have been necessary to take account of any PEEPi in calculating resistance and elastance, but it was never seen in our patients. In order to avoid absorption atelectasis, the lungs were ventilated with 30% oxygen in nitrogen [16].

At each experimental time, at least one end-expiratory occlusion followed by at least three end-inspiratory occlusions were performed. All the occlusions were separated by five tidal breaths. As the ventilatory mechanics are frequency-, flow- and volume-dependent [5], all the subjects underwent ventilation of the lungs with the same pattern: frequency 15 b.p.m., *V*T = 0.6 litre, inspiratory time (*T*I) 1 s, expiratory time (*T*E) 3 s.

The study was performed in the operating theatre, before the beginning of the surgical procedure. Midazolam 5 mg i.m. was given as premedication. Anaesthesia was induced with methohexitone 2.85 (SD 0.5) mg kg^{-1} and maintained with a continuous infusion of this drug (0.1 mg kg^{-1} min^{-1}). Neuromuscular block was produced with vecuronium 0.15 mg kg^{-1} and monitored with train-of-four stimulation of the adductor pollicis muscle. A surgical level of paralysis was observed in every subject during the duration of the study. The trachea was intubated with the orotracheal tube described above, the lungs were ventilated manually in order to achieve a standard volume history and the patient was connected to the ventilator. Six minutes later, the first group of occlusions were recorded (T_0: baseline values). A first dose of fentanyl 4.9 (0.4) µg kg^{-1} was given and a second group of occlusions (T_1) was recorded 6 min later. A second dose of fentanyl 1.75 (0.3) µg kg^{-1} was given together with atropine 1 mg. The last group of occlusions (T_2) was performed 6 min later. The duration of the study did not exceed 25 min and recovery was always uneventful.

Statistical analysis

Data are given as mean (SD). Means were compared with a non-parametric Friedman test and Wilcoxon signed-rank tests. $P < 0.05$ was considered to be significant.

RESULTS

After administration of fentanyl, all the measured resistances increased significantly: *R*max ($P = 0.005$), *R*aw ($P = 0.017$) and ΔR ($P = 0.005$) (table I). The increase in *R*aw paralleled the increase in ΔR, because the contribution of ΔR to *R*max remained stable: 56% at T_0 and 56.8% at T_1 ($P = 0.87$). While *E*st remained stable during the whole study, *E*dyn increased slightly (+6.4%) ($P = 0.005$) with fentanyl (table II).

When atropine was added to fentanyl, *R*aw decreased significantly ($P = 0.007$) and returned to its control value ($P = 0.17$). However, ΔR at T_2 remained stable compared with its value at T_1 ($P = 0.14$) but was significantly greater than at T_0 ($P = 0.012$); its contribution to *R*max increased significantly ($P = 0.028$) between T_1 and T_2 and was significantly greater at T_1 than at T_0 ($P = 0.01$). The decrease in *R*max at T_2 was significant compared with those at T_1 ($P = 0.005$) and T_0 ($P = 0.04$). *E*dyn remained stable between T_1 and T_2 ($P = 0.64$) (table II).

DISCUSSION

We have found that, in anaesthetized, paralysed patients undergoing mechanical ventilation, fentanyl increased all the measured resistances. There was a parallel increase in *R*aw and ΔR, their respective contribution to *R*max remaining stable. When atropine was given, *R*aw decreased and returned to the control value, while the contribution of ΔR to *R*max increased.

We have used the end-inspiratory occlusion method [7]; this allows separation of airway resistance (*R*aw) from the non-Newtonian, peripheral resistance (ΔR). As ΔR varies with the ventilatory pattern [5], we maintained the same pattern in all patients, to allow comparison of resistances. The tracheal pressure was measured within the airway, in order to avoid subtraction of the tracheal tube resistance from the resistance values [14]. Any occlusion has a finite time, and allows a residual flow [17]. The volume resulting from this residual flow can be estimated as 2.5 % of V_T, according to the calculations of Kochi and colleagues [18], who have studied ventilatory mechanics in cats with the same occlusion method and a very similar ventilator (Servo Ventilator 900 C). This leads to underestimation of the initial pressure change and thus of the values of *R*max and *R*aw. However, each subject acted as his own control and this allowed at least a qualitative comparison.

General anaesthesia and paralysis were obtained with methohexitone and vecuronium, respectively. It could be argued that these drugs might have modified bronchial size and reactivity. However, neither of these drugs induces measurable liberation of histamine [19, 20], and vecuronium does not interact with the muscarinic receptor of the bronchial autonomic innervation [20]. Moreover, because fentanyl does not induce detectable liberation of histamine in plasma [21] or the tissues [22], we can postulate that the changes in resistance observed during the study were probably caused by the direct effect of fentanyl.

A second dose of fentanyl was given before the T_2 measurements in order to avoid an excessive decrease in plasma concentration of fentanyl. After a loading dose, there is a second distribution of fentanyl, with a half-life ($T_{\frac{1}{2}}{}^{\alpha}$) of 10–30 min, but with a wide variability in individual pharmacokinetics [23]. A second dose (1.75 $\mu g\ kg^{-1}$), is then able to maintain a relatively great plasma concentration of the drug [23]. Thus the effect of fentanyl on resistances would not be declining with time, and the observed values at T_2 could be attributed to the antagonism by atropine of the effect of fentanyl.

The baseline values of *R*max, *R*aw, ΔR and *E*st were in the range of values calculated from the data of D'Angelo and colleagues [5], who studied adult subjects anaesthetized with enflurane and nitrous oxide and paralysed with pancuronium. In our study, with fentanyl, *R*max and its two components, *R*aw and ΔR, increased. An increase in *R*max with a similar dose of fentanyl during thiopentone anaesthesia was described by Cigarini and colleagues [3]. In their study, such an increase in *R*max with fentanyl did not occur during anaesthesia with propofol. However, these authors did not partition *R*max. The initial component of *R*max is *R*aw. The increase in our study could have been caused by a reduction in FRC which is observed commonly after induction of general anaesthesia [1]. In fact, the observed stability of *E*st suggests that such a change was negligible during the short duration of our study. Moreover, D'Angelo and colleagues [5] have shown that ΔR varies in the same direction as lung volume. In our study, ΔR increased with fentanyl. Thus the increase in *R*aw resulted from bronchoconstriction and not a reduction in lung volume. Moreover, the increase in the initial pressure change after occlusion after a bronchoconstrictive challenge reflects an effective increase in *R*aw, despite introduction of significant mechanical heterogeneities in the lung, as shown by Ludwig and colleagues [24]. Because *R*aw decreased with atropine, which blocks all muscarinic responses within the bronchial tree with equal efficacy [25], it is suggested that the observed effect of fentanyl on the bronchial muscle was vagally induced.

The second component of *R*max is the additional resistance, ΔR, that may result from the viscoelastic properties of the respiratory system, variation in regional time constants, or both. As *E*st remained stable, the increase in ΔR was probably not caused by variation in lung volume. Moreover, in spite of the bronchodilatation induced by atropine, ΔR did not change. This suggests that the bronchoconstrictor effect of fentanyl did not induce significant variations in regional time constants that could have explained the increase in ΔR observed at T_1. Consequently, it can be argued that fentanyl acts directly on pulmonary viscoelastic properties [26]. An effect of thoracic and abdominal muscles is excluded, because of the presence of neuromuscular block. Thus fentanyl increased peripheral resistance, possibly through an effect on peribronchiolar contractile structures [27]. These structures are independent of the parasympathetic system and are insensitive to atropine because there are few muscarinic receptors in terminal bronchioles [23].

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ACCURACY OF COAGULATION STUDIES PERFORMED ON BLOOD SAMPLES OBTAINED FROM ARTERIAL CANNULAE

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SUMMARY

We have assessed the accuracy of coagulation studies in blood obtained from intra-arterial cannulae. Paired samples were studied in blood from 39 patients receiving intensive care; one sample was obtained by venepuncture and the other from an intra-arterial cannula after the apparatus deadspace plus 5 ml of blood had been discarded. Activated partial thromboplastin time (APTT) (with thromboplastin routinely used in our laboratory), prothrombin time (PT), thrombin time (TT), fibrinogen and heparin assays were measured on each sample. In 37 sample pairs, APTT was measured also using a different thromboplastin. The median difference between the sample pairs was 5.5 s for APTT ($P = 0.032$*) and 1.0 s (*$P = 0.048$*) for TT, the times for arterial cannula samples being longer. There was no significant difference between arterial cannula and venepuncture samples for PT or fibrinogen concentration. Heparin assays revealed heparin contamination in samples obtained from arterial cannulae in 15 of 30 patients not receiving heparin. It is concluded that, when coagulation studies are performed using the techniques used routinely in our laboratory, a blood sample from an arterial cannula may give clinically misleading information because of contamination with small amounts of heparin, and that separate venepuncture is recommended.* (Br. J. Anaesth. 1992; **69**: 599–601)

KEY WORDS

Blood: arterial samples, coagulation tests.

Critically ill patients require repeated blood samples for a wide range of laboratory investigations. It is humane to avoid separate venepuncture by withdrawing blood for laboratory investigations from an indwelling arterial cannula if present. There has been concern that heparinized saline used to maintain the patency of such systems contaminates blood samples, resulting in clinically misleading information when coagulation studies are performed [1, 2]. Recent work [3] has suggested that if 5 ml of blood is withdrawn from an arterial cannula before the sample for coagulation testing is withdrawn, clinically accurate results are obtained. Our impression in this hospital was that this was not so. We have therefore re-examined this question.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee, and consent for blood sampling obtained from either the patient or the next of kin. Paired blood samples were taken from 39 unselected patients with a wide range of illness in the adult intensive care unit. Patients with and without previously identified coagulopathies (including anticoagulant administration) were included. All the patients had previously had an arterial cannula (20-gauge Quickcath, Baxter) sited for monitoring. This was connected to a continuous flush device (Intraflo, Abbott Critical Care Systems), which flushed the cannula with heparinized saline 2 u ml^{-1} at 3–5 ml h^{-1}. In each patient, venepuncture was performed in a limb other than that in which the arterial cannula was sited, and 4.5 ml of blood withdrawn. Venepuncture was not performed in a limb in which an i.v. infusion was sited. A 4.5-ml sample from the arterial cannula was withdrawn immediately after 5.0 ml plus apparatus deadspace (0.6 ml) had been withdrawn through the cannula and discarded. Each sample was placed in a stoppered plastic tube containing 0.109 mol $litre^{-1}$ trisodium citrate 0.5 ml and transported to the haematology laboratory for assay. All the samples were taken by one of the authors (S.R.H.).

The samples were labelled such that, until completion of the study, laboratory staff were unaware of how the samples had been obtained.

Plasma was obtained from each sample by centrifugation at 2000 *g* at a temperature of 4 °C for 30 min. This technique maximizes platelet removal and minimizes any release of platelet factor 4, which shortens the activated partial thromboplastin time (APTT) [4]. The APTT was measured using the technique described by the U.K. Reference Laboratory for Anticoagulant Reagents and Control [personal communication to individual laboratories]. This was carried out manually in a water bath maintained at 37 °C, using the "Manchester" reagent (Manchester Comparative Reagents Ltd), the test tube being tilted repeatedly and the time noted

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until observed formation of fibrin clot. The prothrombin time (PT) was also measured manually, using the Manchester reagent for PT assay (Manchester Thrombosis Research Foundation). Fibrinogen assay was performed according to the technique described by Clauss [5] and thrombin time (TT) was also measured manually in a heated water bath after addition of working thrombin solution to the sample plasma. All of these measurements were carried out in duplicate on each sample, the reported result being the mean of the two results. Heparin assays were by the method of Teien and Lie [6].

The APTT was measured also using an alternative thromboplastin (Diagen B & A) on 37 sample pairs.

Mann–Whitney U tests were used to assess statistical significance. Statistical calculations were performed with the Minitab 7.2 statistical software package, on an Olivetti PCS 286 computer using the MS DOS 3.3 disk operating system.

RESULTS

Normal values for coagulation tests in this hospital's haematology laboratory were derived from analysis of 30 "normal" samples (table I). The values obtained for APTT, PT, TT and fibrinogen concentration from the two groups of paired samples are shown in table II. Both the median APTT and median TT were both prolonged significantly in the samples from the arterial cannulae. There was no significant difference between the two groups in PT or fibrinogen concentration. APTT measured using Diagen B & A thromboplastin was also prolonged significantly in samples taken from arterial cannulae (table II).

TABLE I. *Laboratory normal values (95% CI)*

PT (s)	15.7 (14–18)
APTT (s)	
Manchester reagent	42.5 (35–50)
Diagen B & A	38.5 (34–48)
TT (s)	10–14
Fibrinogen (g litre^{-1})	2.5–4.0

The APTT (Manchester reagent) was prolonged by 20–49% in the arterial relative to the venepuncture samples in 10 (26%) of the 39 patients studied, and by 50% or more in six (16%) patients.

Six patients had received heparin either during haemodialysis or during aortic surgery, and an additional three had received low molecular weight heparin. The heparin assays from these nine patients were examined separately. In 28 of the remaining 30 patients, heparin was present in concentrations equal to or less than the level of detection in the samples obtained by venepuncture (range < 0.03–0.07 u ml^{-1}). In contrast, heparin was present in measurable amounts in 15 of the 30 arterial samples obtained from these patients (range < 0.03–0.19 u ml^{-1}).

The median (range) for the APTT in the 15 arterial samples demonstrably contaminated with heparin was 58 (30.5–88.5) s, compared with 39 (29–51.5) s in the venepuncture samples ($P = 0.0026$, 95.4% confidence interval (CI) for difference 6.5–28.3 s). The median (range) for TT in the arterial samples from these other patients was 14 (11–20) s, compared with 12 (10–15) s in the venepuncture samples ($P = 0.0154$, 95.4% CI for difference 0–2 s).

There was no significant difference in either APTT or TT between the sample pairs taken from the nine patients who had received either low molecular weight heparin or heparin.

TABLE II. *Results for PT, APTT (Manchester reagent), APTT (Diagen B & A), TT and fibrinogen. †Mann–Whitney U test*

	Arterial cannula	Venepuncture	Inter-sample difference	P†
Prothrombin time (s) ($n = 39$)				
Median	19.5	18.5	0.0	
Range	15.0–26.5	15.0–33.0	−6.5–3.5	ns
Inter-quartile	17.0–20.5	16.5–21.0	−0.5–1.0	
APTT (Manchester) (s) ($n = 39$)				
Median	45.0	36.5	5.5	
Range	30.0–108.0	29.0–72.5	−9.0–38.5	0.032
Inter-quartile	34.5–59.5	32.5–44.0	0.0–19.0	
95.1% CI			0.5–11.0	
APTT (Diagen B & A) (s) ($n = 37$)				
Median	40.0	37.0	4.0	
Range	26.0–120.0	26.5–82.0	−5.0–72.0	0.024
Inter-quartile	34.0–59.0	32.8–40.5	1.0–19.3	
95.1% CI			0.5–13.0	
Thrombin time (s) ($n = 39$)				
Median	13.0	12.0	1.0	
Range	9.0–60.0	10.0–60.0	−5.0–34.0	0.048
Inter-quartile	11.0–16.0	12.0–13.0	0.0–2.0	
95% CI			0.0–2.0	
Fibrinogen (g litre^{-1}) ($n = 39$)				
Median	4.3	3.7	0.0	
Range	1.5–6.8	1.5–6.4	−0.8–2.7	ns
Inter-quartile	2.8–5.4	2.5–5.0	−0.1–0.4	

DISCUSSION

Blood sampling from arterial cannulae for laboratory investigations is common practice in intensive care units. This is convenient for the medical staff and avoids patient distress caused by repeated venepuncture. When coagulation studies are performed on such samples, the validity of the results obtained has been questioned because of heparin contamination [1, 2]. Heparin inhibits coagulation factors involved in the intrinsic part of the coagulation cascade, thus prolonging the APTT. It interacts also with thrombin to inhibit catalysis of the conversion of fibrinogen to fibrin, thus prolonging the TT.

Some authors have suggested that samples from arterial cannulae may give valid results if appropriate measures are taken to prevent heparin contamination [3, 7–11]. The largest volume recommended among these studies was 5 ml plus apparatus deadspace [3], and we decided to use this volume in our study rather than introduce differing discard volumes as another variable. None of the aforementioned studies took adequate consideration of which reagents and laboratory techniques were used when performing coagulation tests, although it is known that different reagents and different techniques have different sensitivities to heparin [12–14].

The Manchester and Diagen B & A thromboplastins used in our study for performing the APTT are used in a significantly large proportion of haematology laboratories in the United Kingdom [15].

An APTT of less than 40 s (> 5 % less than the laboratory mean normal time) was present in 24 (61.5 %) of the 39 venepuncture samples. This confirms previous findings that coagulation factors are produced as part of the physiological response to stress [16], the patients in our study being either critically ill, or having recently undergone major surgery.

We have demonstrated that, even though what were previously thought to be adequate volumes of blood may be discarded in the procedure for sampling from arterial cannulae, minute amounts of heparin may still contaminate such a blood sample, resulting in a significant likelihood of prolongation of the APTT and TT. We believe that this difference was clinically significant in the 16 patients in whom the APTT was prolonged by 20 % or more relative to the venous sample. This may be to the extent that there is unnecessary administration of blood products to the patient. It is apparent that, despite utmost care taken to adopt a uniform sampling technique during the course of this study, contamination by measurable amounts of heparin of blood samples obtained from arterial cannulae occurs in 50 % of cases, suggesting that heparin contamination of such samples is both frequent and unpredictable.

We suggest that either a separate venepuncture is used when obtaining blood for coagulation studies from patients in Intensive Care Units, or potential contamination with small quantities of heparin is assumed. If there is no alternative to obtaining blood samples for coagulation studies from an arterial cannula, the maximum feasible volume of deadspace blood should be withdrawn initially, and the haematology laboratory should be informed of the source of the blood sample.

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ISOFLURANE DOES NOT INCREASE THE INCIDENCE OF INTRAOPERATIVE MYOCARDIAL ISCHAEMIA COMPARED WITH HALOTHANE DURING VASCULAR SURGERY

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SUMMARY

*We have studied the incidence of new intraoperative myocardial ischaemia (IMI), myocardial infarction (MI) and cardiac death (CD) in 500 consecutive patients undergoing elective major non-cardiac vascular surgery. Patients were allocated randomly to receive either halothane (*n = 226*) or isoflurane (*n = 274*) as principal anaesthetic agent. Using real-time ST segment trend analysis (leads V5 and II) IMI (halothane 39%, isoflurane 38%), MI (halothane 1.3%, isoflurane 1.5%) and CD (halothane 0.4%, isoflurane 0.7%) did not differ significantly between the two groups. Twenty-three per cent of IMI episodes were related to haemodynamic disturbances, but unrelated to the type of surgery: 148 supra-aortic (IMI = 39%), 244 abdominal aortic (IMI = 41%) and 108 lower extremity revascularizations (IMI = 33%). We conclude that the choice of volatile anaesthetic agent does not influence cardiac morbidity or mortality in this type of patient.* (Br. J. Anaesth. 1992; **69**: 602–606)

KEY WORDS

Anaesthetics, volatile: halothane, isoflurane. Complications: intraoperative myocardial ischaemia. Heart: myocardial infarction. Surgery: vascular.

Isoflurane has been shown to have either beneficial or deleterious effects on myocardial oxygenation in animal and human studies [1–5]. Three large prospective outcome studies in patients undergoing coronary artery bypass grafting (CABG) [6–8] have shown conflicting results. Although the "CABG-model" provides a relatively homogeneous patient population, cardiopulmonary bypass, the adequacy of cardioplegia and myocardial revascularization may have important but independent effects on new intraoperative myocardial ischaemia (IMI) and outcome. Moreover, these studies may not be applicable to the greater number of non-cardiac patients with suspected or proven ischaemic heart disease (IHD). In patients undergoing major non-coronary vascular procedures, IHD is the principal factor determining early and late cardiac morbidity and mortality [9]. Because a significant relationship has been demonstrated between the incidence of new ischaemic episodes and the occurrence of postoperative myocardial infarction (MI) [10, 11], we have examined the role of the primary anaesthetic agent on the incidence of new IMI in 500 vascular surgical patients who were prospectively allocated randomly to receive either isoflurane or halothane.

PATIENTS AND METHODS

After obtaining approval from our institutional board and informed consent from each patient, we studied 500 consecutive patients undergoing elective vascular procedures. These patients underwent one of three types of peripheral vascular surgical procedure: 244 abdominal aortic reconstructions (abdominal aortic aneurysmectomy using the graft-inclusion technique, aorto–bifemoral or bi-iliac bypass, aortic or transaortic renal artery endarterectomy); 148 supra-aortic reconstructions (carotid, subclavian or vertebral artery endarterectomy and aorto–brachiocephalic trunk bypass); 108 lower extremity arterial revascularizations (iliac and femoral artery reconstruction, or femoro–femoral or femoro–crural saphenic vein bypass). Two staff anaesthetists (K.D.S. and B.M.) and five staff vascular surgeons participated in this study as part of their regular clinical duties between November 1, 1988 and July 31, 1990. Assignment of an anaesthetist to a patient in this study was by chance alone.

Preoperative patient characteristics, long-term medication and cardiac history are listed in table I. All patients were classified using the grading score for angina pectoris of the Canadian Cardiovascular Society [12]. The classification was modified by grouping patients without angina pectoris (AP0) and asymptomatic patients (APA) with silent ischaemia, unknown previous MI, or both, but with signs present in the preoperative ECG.

A standard 12-lead ECG (50 mm s^{-1}; 10 mm = 1 mV) was recorded on the day before surgery. Each patient was visited before operation by the anaesthetist. Approximately 2 h before scheduled induction of anaesthesia, flunitrazepam 1–2 mg and the respective anti-anginal or antihypertensive medications, or both, were administered orally.

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TABLE I. *Preoperative characteristics. ACBG = aorto-coronary bypass grafting; PTCA = percutaneous transluminar coronary angioplasty*

	Halothane ($n = 226$)	Isoflurane ($n = 274$)	P
Age (yr)	61 (38–83)	58 (43–83)	
Age > 60 yr (%)	60.8	57.8	0.58
Sex (M:F)	164:62	224:50	0.029
Preoperative medication (%)			
Beta blocking agents	18.1	16.4	0.75
Calcium antagonists	45.1	42.3	0.58
Nitrates	20.4	23.7	0.29
Antihypertensives	20.4	22.3	0.52
Cardiac history (%)			
History of MI	28.8	25.9	0.53
Previous ACBG/PTCA	5.3	7.3	0.27
No angina pectoris (AP0)	38.2	34.2	0.37
Asymptomatic angina (APA)	13.9	14.2	0.75
Typical angina pectoris			
API	13.4	9.9	0.27
APII	20.5	24.5	0.22
APIII	11.0	11.5	0.65
APIV	2.7	5.1	0.1

Anaesthesia was induced with thiopentone 2–4 mg kg^{-1} i.v. and neuromuscular block was produced with vecuronium 0.1 mg kg^{-1} initially for tracheal intubation. Anaesthesia was maintained with halothane or isoflurane and 50% nitrous oxide in oxygen and supplemented with small to moderate doses of fentanyl (less than 6 µg kg^{-1} for the entire operation), depending on surgical requirements.

Halothane was administered on even-numbered days and isoflurane on odd-numbered days during the first 1 yr and *vice versa* in the second half of the study. The inspired concentration of the volatile agent was adjusted to maintain the arterial pressure at a value determined by the anaesthetist. Halothane was not used in patients in whom liver enzyme concentrations were increased or where halothane had been given within the preceding 4 weeks [13].

Normoventilation was produced as assessed by capnography and blood-gas analysis.

Neither anaesthetic nor surgical techniques changed during the 21-month period of the study. If, despite adequate anaesthesia, vasodilatators were needed, either nitroglycerin or nifedepine was used, depending on clinical circumstances.

After arrival of the patient in the operating room, ECG leads were attached and a seven-lead ECG (I, II, III, avR, avL, avF, V5) was recorded with a standardization of 1 mV = 10 mm. The ST segment trends of lead II and V5 were monitored continuously 80 ms after the J-point of the QRS complex (Sirecust 1280, Siemens AG, Erlangen, Germany) from the beginning of the preanaesthetic preparation until the patient left the operating room. Leads II and V5 calibrated to 10 mm mV^{-1} were recorded at 25 mm s^{-1} for 15 s when the ST segment trend analysis was suggestive of ischaemia. The recording system (Sirecust D 220, Siemens AG, Erlangen, Germany) complied with the recommendations of the American Heart Association (diagnostic quality, 0.05–100 Hz). The 12-lead ECG which had been recorded the day before surgery was used as a reference.

Ischaemia was diagnosed by the observer using the continuous ST segment trend analysis as new reversible horizontal or downsloping ST segment depression of at least 0.1 mV or ST segment elevation of at least 0.2 mV at J point + 80 ms lasting for at least 1 min.

Arterial pressure and heart rate were noted when ischaemia was diagnosed and compared with values taken 2 min before the event. In addition, when a flow-directed pulmonary artery catheter was used (38 of 500 patients) myocardial ischaemia was considered present when wedge pressure recordings showed an abnormal AC wave > 15 mm Hg or V wave > 20 mm Hg [14].

All ECG recordings were reviewed after operation by one investigator who was unaware of the patient and of the principal anaesthetic used.

In case of IMI, treatment was commenced immediately after ECG traces were recorded and according to the probable cause. Hypotension (systolic pressure < 90 mm Hg) in combination with blood loss was treated by fluid replacement and decrease of inspired volatile anaesthetic concentration; hypertension (systolic pressure > 180 mm Hg) by increase of anaesthetic depth (increasing inspired volatile anaesthetic concentration or administration of fentanyl followed by nitroglycerin or nifedepine); tachycardia (> 110 beat min^{-1}) (after excluding hypovolaemia) by increase of anaesthetic dose as above, followed by pindolol 80 µg i.v.; and ischaemia without haemodynamic disturbances by administration of nitroglycerin.

In the postoperative period, serial 12-lead ECG recordings, serum creatine kinase (CK) and myoglobin fraction (CKMB) concentrations were measured in samples obtained immediately after surgery and 12 and 24 h later. MI was considered present if ECG changes (new persistent Q waves of at least 0.04 s duration in the absence of bundle branch blocks or major QRS axis changes) were found or CKMB concentrations were in excess of 10% of CK concentrations or greater than 40 u $litre^{-1}$. Cardiac death (CD) was diagnosed if the patient died from arrhythmias or congestive heart failure.

Statistics

Data were collected, stored and analysed on an Intel 80386-based microcomputer using the Statistical Package for the Social Sciences (SPSS/PC). Chi-square analysis of significance was calculated for frequency data of the halothane and isoflurane groups (in case of MI and CD, Fisher's exact test because of the small number of patients). The data were expressed as mean (SD) for normally distributed variables (heart rate and mean arterial pressure using the Shapiro–Wilks and Lilliefors test). Data were compared by Student's t test for unpaired data between both groups in the three types of surgery. $P < 0.05$ was considered statistically significant.

RESULTS

At completion of our study, 274 patients had received isoflurane and 226 halothane as their primary anaesthetic agent. Both groups were comparable—

TABLE II. *Perioperative complications and outcome in 500 vascular patients*

	Halothane ($n = 226$)	Isoflurane ($n = 274$)	P
New intraoperative ischaemia	88 (38.9%)	105 (38.3%)	0.89
associated with			
Tachycardia (> 110 beat min^{-1})	25 (11%)	25 (9%)	0.57
Hypertension (> 180 mm Hg)	14 (6%)	16 (6%)	0.87
Hypotension (< 90 mm Hg)	16 (7%)	22 (8%)	0.69
Myocardial infarction	3 (1.3%)	4 (1.5%)	0.9
Cardiac death	1 (0.4%)	2 (0.7%)	0.68

TABLE III. *Perioperative myocardial ischaemia*

	Halothane (%)	Isoflurane (%)	P
Myocardial ischaemia observed during			
Arrival	8.4	8.8	0.97
Anaesthetic induction	5.3	6.9	0.45
Surgical stimulation	22.6	23.7	0.74
Tracheal extubation	10.6	7.7	0.25

with the exception of sex—in preoperative cardiac assessment, medication and characteristics (table I). Before operation, more than 60% of patients in both groups had ECG or clinical signs of IHD and were at risk of perioperative MI.

The incidence of new IMI, MI and CD did not differ between the two groups (table II).

About 23% of all ischaemic episodes in both groups were linked with haemodynamic disturbances such as tachycardia (heart rate > 110 beat min^{-1}) (halothane 11%, isoflurane 9%), hypertension (systolic arterial pressure > 180 mm Hg) (halothane 6%, isoflurane 6%) or hypotension (systolic arterial pressure < 90 mm Hg) (halothane 7%, isoflurane 8%). In the anaesthetic room, about 8% (halothane 8.4%, isoflurane 8.8%) of the patients had acute new ischaemia (ST segment depression or elevation, prominent V waves and increased pulmonary capillary wedge pressure without chest discomfort—that is, silent angina), which were at least partly reversible during anaesthesia and surgery (table III).

During induction of anaesthesia, about 6% of the patients had new ischaemic episodes, with no difference between the halothane and isoflurane groups. Approximately 23% of all patients had new reversible episodes of MI during surgery, while 8% of the isoflurane group and 11% of the halothane patients had ischaemic changes during and immediately after tracheal extubation.

Abnormal A and V waves indicative of new myocardial ischaemia appeared in only two of 30 patients (6.7%) without ST segment changes.

Table IV summarizes the haemodynamic changes (mean (SD)) during the occurrence of acute IMI in relation to the three types of vascular surgical interventions. The incidence of new myocardial ischaemia was similar in the three groups. There were no significant haemodynamic changes during the ischaemic episodes, and the extent of these changes was unrelated to the type of surgery.

DISCUSSION

We have found that the risk of myocardial ischaemia, perioperative myocardial infarction, and fatal cardiac outcome during anaesthesia was similar when either halothane or isoflurane was used as the primary anaesthetic for major non-cardiac vascular procedures. As the study was designed to mimic clinical practice, the effects of nitrous oxide and fentanyl were not analysed separately because the doses of these drugs did not differ between the groups.

TABLE IV. *Haemodynamic observations before and during new intraoperative myocardial ischaemia (IMI) in three types of vascular surgery (mean (SD) or No. (%)).* † *Obtained 2 min before onset of new intraoperative myocardial ischaemia*

	Halothane		Isoflurane	
	Control value†	Changes during IMI	Control value†	Changes during IMI
Supra-aortic surgery	($n = 73$)	(IMI = 43.8%)	($n = 75$)	(IMI = 34.7%)
Heart rate (beat min^{-1})	82 (20)	5 (1)	84 (23)	4 (1)
Mean arterial pressure (mm Hg)	92 (15)	−1 (1)	95 (21)	−2 (5)
No. (%) of patients with				
heart rate > 110 beat min^{-1}	3 (4.1)	9 (12.3)	5 (6.7)	8 (10.7)
systolic arterial pressure > 180 mm Hg	4 (5.5)	5 (6.8)	4 (5.8)	6 (8)
systolic arterial pressure < 90 mm Hg	1 (1.4)	5 (6.8)	0	6 (8)
Aortic surgery	($n = 112$)	(IMI = 36.6%)	($n = 132$)	(IMI = 40.6%)
Heart rate (beat min^{-1})	78 (20)	3 (2)	78 (18)	4 (1)
Mean arterial pressure (mm Hg)	84 (20)	9 (6)	84 (17)	−2 (2)
No. (%) of patients with				
heart rate > 110 beat min^{-1}	3 (2.7)	11 (10.7)	5 (3.8)	12 (9.1)
systolic arterial pressure > 180 mm Hg	3 (2.7)	7 (6.3)	0	7 (5.3)
systolic arterial pressure < 90 mm Hg	5 (4.5)	8 (7.1)	7 (5.3)	11 (8.3)
Infra-aortic surgery	($n = 41$)	(IMI = 36.6%)	($n = 67$)	(IMI = 31.3%)
Heart rate (beat min^{-1})	82 (16)	5 (5)	77 (12)	5 (4)
Mean arterial pressure (mm Hg)	87 (21)	−1 (0.4)	88 (17)	−2 (2)
No. (%) of patients with				
heart rate > 110 beat min^{-1}	1 (2.4)	3 (7.3)	0	5 (7.5)
systolic arterial pressure > 180 mm Hg	0	2 (4.9)	1 (1.5)	3 (4.5)
systolic arterial pressure < 90 mm Hg	3 (3.7)	3 (7.3)	1 (1.5)	5 (7.5)

There were no significant differences between the groups with respect to any factors known to influence IMI (patient age or preoperative ischaemia, arterial pressure and drug therapy, anaesthetic technique or anaesthetist). All cases were undertaken at one institution by two anaesthetists. The prevalence of spontaneous transient impairment of myocardial oxygen supply [15] in the groups could not be compared, but is unlikely to differ, as the groups were comparable for severity of myocardial ischaemia and were similar to those described previously [16–19].

However, the incidence of cardiac deaths and myocardial infarction was too small to reveal outcome differences between the primary anaesthetics but, assuming that the incidence of adverse and fatal outcome remained constant we would need more than 10000 patients (i.e. 35 years) to observe statistically significant differences between patients having received halothane or isoflurane as a primary anaesthetic.

The incidence of MI and fatal cardiac outcome was less than in previous studies [5, 11]. This may be attributable to the use of an on-line ST segment trend analyser and immediate provision of therapy.

The poor correlation between IMI and haemodynamic disturbances confirms previous studies [7, 10, 15, 20] and is the probable explanation for the similarity of IMI in the different operation groups. The haemodynamic changes associated with vascular cross-clamping and declamping are much greater for the aorta than for peripheral vessels, but other factors appear to be of greater importance.

Previous studies have suggested that anaesthetic agents *per se* might cause or contribute to myocardial ischaemia under certain circumstances; controversy exists, however, on whether isoflurane alone or in combination with nitrous oxide or fentanyl has deleterious effects on the coronary circulation and outcome in IHD patients [2, 4, 8, 21, 22]. In particular, because isoflurane acts as a coronary arteriolar dilatator it may induce coronary steal [21, 22]. In contrast to prospective and retrospective clinical trials [5–7, 23], halothane appeared preferable to isoflurane in pharmacological studies [4, 21, 22]. While the latter drug was thought to induce maldistribution (steal) in CABG patients [4], especially in the presence of hypotension [22], recently published data have failed to support this belief: Slogoff and colleagues [23] demonstrated that the incidence of IMI did not differ between halothane and isoflurane groups in more than 900 CABG patients with a steal-prone coronary anatomy. In contrast, Inoue and colleagues reported a causal relationship between the incidence of MI and the number of deaths and isoflurane anaesthesia compared with enflurane in 1178 CABG patients [8]. However, the incidence of fatal IMI was only 43% (six of 14) of total mortality and the majority of adverse outcomes could not be attributed directly to the primary anaesthetic, as there were group differences in the requirement for antihypertensive drugs, the use of catecholamines or inotropic drugs and the need for intraoperative balloon pump assistance after cardiopulmonary bypass. Moreover, most perioperative MI occurred in the majority of studies 12–72 h after operation, and factors such as unsuccessful weaning, early tracheal extubation, discontinuation of supplementary oxygen, inadequate analgesia and stress during postoperative intensive care may also be important [4, 5].

We conclude that many other factors are probably more important than the choice of the anaesthetic as determinants of myocardial ischaemia and cardiac mortality in vascular surgical patients.

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EVALUATION OF CLOSED LOOP CONTROL OF ARTERIAL PRESSURE DURING HYPOTENSIVE ANAESTHESIA FOR LOCAL RESECTION OF INTRAOCULAR MELANOMA

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SUMMARY

We have studied 20 patients undergoing local resection of intraocular melanoma during hypotensive anaesthesia, allocated randomly to receive either manual control by an experienced anaesthetist or closed-loop computer control of an infusion of a 5:1 mixture of trimetaphan camsylate (TMP) and sodium nitroprusside (SNP). There were no significant differences in the smallest systolic and diastolic arterial pressures obtained, heart rate or infusion requirements between the two groups, but the duration of both the infusion and the operation were significantly longer in the computer-controlled group ($P < 0.05$). The quality of control of arterial pressure was assessed by the percentage of time spent at pressures greater and less than the prescribed target values, and was satisfactory in both groups during the critical period of profound hypotension. We conclude that the computer-controlled infusion performed satisfactorily during profound hypotension compared with an experienced anaesthetist. (Br. J. Anaesth. 1992; **69**: 607–610)

KEY WORDS

Anaesthetic techniques: hypotensive anaesthesia, manual control, closed-loop computer control.

Patients undergoing local resection of intraocular melanoma require intraoperative arterial pressure control to a systolic pressure of 40±5 mm Hg during the period of choroid dissection. Hypotension to this degree is required to prevent intraocular haemorrhage from the vascular choroid, which may affect visual outcome [1, 2]. Precise control of arterial pressure during this period is essential, combined with meticulous monitoring of the adequacy of cerebral and myocardial perfusion.

Control of arterial pressure by closed-loop infusion of vasodilators has been shown to compare favourably with the control achieved by intensive therapy staff in postoperative cardiac surgical patients [3–6]. Automatic control of arterial pressure has also been used during operation and was shown to compare favourably with manual control by the anaesthetist [7–10].

We have compared the quality of induced hypotension by computer-controlled infusion with that achieved manually by an experienced anaesthetist during local resection of choroidal melanoma.

PATIENTS AND METHODS

We have studied 20 patients aged between 39 and 66 yr undergoing local resection of intraocular melanoma and considered suitable for hypotensive anaesthesia. Hospital Ethics Committee approval was obtained and informed consent given by all patients.

All patients received the standard anaesthetic for this procedure in this unit [7], including oral atenolol 50–100 mg 90 min before operation, followed by i.m. pethidine 50–100 mg and promethazine 25–50 mg 1 h before surgery. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1} was given to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide and 1% enflurane in oxygen.

Controlled ventilation to an end-tidal carbon dioxide concentration of 3.8–4.2 kPa was facilitated by tubocurarine and a 10° head-up tilt was used. The dose of tubocurarine was titrated using the Datex Relaxograph to maintain the first twitch response to a train-of-four stimulation (T1) at less than 15% of control. Antagonism of neuromuscular block was achieved with neostigmine and glycopyrronium.

Systolic arterial pressure was controlled by an infusion of sodium nitroprusside (SNP) 200 µg ml^{-1} and trimetaphan camsylate (TMP) 1 mg ml^{-1} in 5% glucose [11–12]. Patients were allocated randomly to two groups: in the manual group, the infusion rate was adjusted manually; in the computer group, the infusion rate was adjusted by a computer-controlled, closed-loop system which comprised an Imed 929 Volumetric pump linked by an Apple IIe microcomputer to the data output of a Datascope 2002 monitor. This system has been described and evaluated previously [3, 5] and consists of a Proportional Integral Derivative controller with adaptive features. The initial infusion rate was calculated by the closed-loop system. After each new cal-

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culation of the infusion rate, the system tracked the rate of change in pressure so that excessive or inadequate decrease caused a further calculation to be made. The raw arterial waveform was scanned by a background subroutine which allowed detection of zeroing, flushing, damping or disturbance of the line. A warning was provided, with an appropriate message for any computer–pump interface errors.

Standard monitoring for this procedure comprised a continuous ECG using the CM5 lead, direct arterial pressure from the radial artery with the transducer at the level of the external auditory meatus, neuromuscular function and end-tidal carbon dioxide concentration. The mean amplitude and zero cross frequency of the EEG were displayed on the Datex Anaesthesia and Brain Activity Monitor (BAM).

During the first 60–90 min, the systolic arterial pressure was reduced gradually to 70–80 mm Hg to allow fashioning of a superficial scleral flap and a vitrectomy to be performed. Profound hypotension to 40±5 mm Hg was then induced before final dissection of a deep scleral flap and incision of the choroid. During this period, ST segment changes and the zero cross frequency of the BAM were used as indicators of global myocardial and cerebral perfusion, respectively. If ST segment depression of greater than 1 mm or a sustained zero cross frequency of less than 5 Hz occurred, the arterial pressure was increased, although this could result in loss of the eye. Nitrous oxide was discontinued 20 min before closure of the scleral flap. After closure of the scleral flap and injection of sulphur hexafluoride gas, the arterial pressure was allowed to increase slowly by less than 5 mm Hg min^{-1} to avoid variations in cerebral blood flow and cerebral oedema. At the end of the procedure anaesthesia was discontinued, neuromuscular block antagonized and the trachea extubated. Patients were kept in the recovery area until obeying commands; i.v. fluids and oxygen were administered until the following day.

Results were analysed using chi-square and the Mann–Whitney *U* tests.

RESULTS

There were no statistical differences between the two groups in age, sex or weight (table I) or in the duration of the period of hypotension, the systolic pressure at induction, the smallest systolic and diastolic pressures obtained, or the smallest mean arterial pressures and heart rates during the period of hypotension in the two groups (table I).

The quality of arterial pressure control was assessed by measuring the percentage of time spent at > ±10% outside the prescribed target pressure. During the entire period of infusion of vasodilator (table II), there were no significant differences in the percentage of time spent at pressures greater than the prescribed target pressure. However, patients in the computer-controlled group spent more time at pressures 10% less than the target pressure ($P < 0.05$). During the period of profound hypotension, there were no significant differences between the two groups in the percentage of time spent at pressures greater and less than the target (table II) and the quality of arterial pressure control was satisfactory in both groups. This may be explained by the smaller reductions in the prescribed target pressure as the critical hypotension was reached, and the corresponding small changes in infusion rate required to achieve the prescribed target.

There were no significant differences in the total amount of SNP or TMP infused in the two groups. Both the duration of the operation and the duration of infusion of vasodilators were longer in the computer-controlled group ($P < 0.05$) (table III). The longer duration of the infusion could be explained by the computer increasing the infusion in smaller increments than the experienced manual

TABLE I. *Patient characteristics (mean (range or SD)) and operative details (median (range))*

	Manual group ($n = 10$)	Computer group ($n = 10$)
Age (yr)	51.4 (31–68)	52.9 (39–68)
Weight (kg)	68.0 (13.6)	70.6 (12.5)
Sex (M/F)	4/6	6/4
Hypotension (min)	90 (50–105)	97.5 (60–130)
Start SAP (mm Hg)	135 (100–200)	127 (100–170)
Smallest SAP (mm Hg)	40 (36–45)	40 (38–42)
Smallest DAP (mm Hg)	21 (18–25)	21.5 (20–32)
Smallest MAP (mm Hg)	27.5 (25–31)	27.5 (20–34)
Heart rate (beat min^{-1})	67 (54–90)	60 (50–75)

TABLE II. *Quality of arterial pressure control throughout the infusion and during profound hypotension (median (range)), expressed as time spent at pressures greater than ±10% outside target pressures.* *$P < 0.05$ *between groups*

	Manual group ($n = 10$)	Computer group ($n = 10$)
During infusion		
Target + 10%	7.69 (2.1–22.4)	8.7 (5.4–13.9)
Target − 10%	10.3 (0–22.4)	22.3 (5.3–27.6)*
During hypotension		
Target + 10%	2.3 (0–6.0)	4.6 (0–14.5)
Target − 10%	6.6 (0–31.8)	2.6 (0–27.7)

TABLE III. *Infusion requirements and intraoperative complications (median (range) or number).* *$P < 0.05$ *between groups*

	Manual group ($n = 10$)	Computer group ($n = 10$)
Infusion requirements		
Total SNP (ml)	8.8 (2.2–13.8)	13.5 (6–41.8)
Total TMP (ml)	44 (11–69)	67.8 (30–209)
Duration of infusion (min)	158 (120–202)	204 (100–268)*
Duration of operation (min)	198 (160–250)	248 (150–285)*
Intraoperative complications		
Oculocardiac reflex:		
Early	2	3
Late	0	0
Both	1	1
ST depression > 1 mm	0	0
Tachycardia	1	0
Increased IOP	1	0
Bleeding during choroid dissection	0	4

operator, and therefore taking longer to achieve any particular target at either induction or offset of the hypotension. However, when the hypotensive target was achieved, the quality and duration of the control were not significantly different from those of the manual control.

The incidence of intraoperative complications was compared in the two groups (table III). There were no significant differences in the incidence of the oculocardiac reflex in the two groups. Adverse changes in the ECG or the ABM did not occur in either group. One patient in the manually-controlled group developed tachycardia requiring treatment with labetalol; an increased intraocular pressure requiring treatment with a 50% aqueous solution of sucrose also occurred in this patient. Despite equally satisfactory control of arterial pressure in both groups during the critical period of profound hypotension, four patients in the computer-controlled group were noted to have some bleeding during the period of choroid dissection. This did not occur in the manually-controlled group.

DISCUSSION

Closed-loop, computer-controlled infusion of vasodilators has been used successfully in the control of hypertension after cardiac surgery [3–6], in which the quality of control achieved by the computer-controlled system has been shown to compare favourably with that achieved manually by nursing staff [3]. Closed-loop computer control of arterial pressure using either volatile agents or vasodilators such as SNP has also been used successfully during operation [7–10], and the control achieved compared favourably with that achieved by the anaesthetist.

We are not aware of any other study in which a combination of SNP and TMP has been infused by a closed-loop, computer-controlled system. The system we used had been used previously to achieve normotension after operation. We have shown that this system can also be used during operation for the production of induced hypotension. Because of variations in operating stages, it was not possible to standardize the time intervals at which changes in target arterial pressure were made or the magnitude of changes in target pressure, and changes were made in response to prevailing surgical conditions. The period of steady-state control of arterial pressure is critical, and the quality of control of arterial pressure during the period of profound hypotension required for dissection of the tumour from the choroid was equally satisfactory in both groups. However, the anaesthetist controlling the infusion in the manually controlled group of patients was experienced in the provision of anaesthesia for this type of surgery and results achieved by a less experienced operator may have compared less favourably with the computer-controlled group.

Despite satisfactory control of arterial pressure in both groups during the period of profound hypotension, four patients in the computer-controlled group were reported to have some minor bleeding during dissection of the tumour from the vascular choroid. This was a subjective assessment made by the surgeon, who was unaware to which group the patient had been allocated. The cause was unclear, but may be related to other factors such as size and position of the tumour or difficulty in dissection, as it was also noted that the duration of operation and infusion of vasodilators was significantly greater in the computer-controlled group. Retrospective analysis of the patient data by the surgeon suggests that, in those patients in whom bleeding was noted, the tumour may have been more difficult to operate upon. Loss of the eye as a consequence of poor operating conditions did not occur in any of the patients. This was a small study, however, and it was not possible to study long-term outcome. Further studies would be required to evaluate this complication in greater detail.

There were no adverse changes on the ECG or the BAM during the operation in either group. All patients were followed up at 6 weeks, 6 months and 1 year. There were no sequelae attributable to hypotension or anaesthesia. Detailed psychometric testing was not carried out, but one patient in the manually controlled group reported mild memory impairment in the early postoperative period. This showed rapid improvement and by 6 weeks the patient was unaware of any impairment of memory function. All patients returned to their previous functional level within the limits of their visual outcome.

We believe that automated control of arterial pressure should only be used under supervision and that careful validation of the input signal must be made. We have found that analysis of the raw arterial waveform allows detection of potential errors such as flushing or disturbance of the arterial line and prevents the system infusing vasodilator in response to an inappropriate signal. In addition, an infusion pump designed for use by computer control should be used to reduce the possibility of incorrect transfer of commands from the computer. With these safeguards, we conclude that a closed-loop, computer-controlled system designed to infuse vasodilators for the control of postoperative hypertension provided satisfactory control of arterial pressure during induced hypotension when compared with a manually controlled infusion.

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EARLY DIAGNOSIS OF ANAPHYLACTIC REACTIONS TO NEUROMUSCULAR BLOCKING DRUGS

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SUMMARY

Neuromuscular blocking drugs (NMB) are involved in most of the anaphylactic reactions occurring during anaesthesia. Patients are evaluated usually 6 weeks after the reaction, by skin testing. In order to obtain an earlier diagnosis, we have measured plasma concentrations of histamine, tryptase and NMB-specific IgE antibodies in 14 patients after an anaphylactoid reaction. We have compared the results with those of skin tests and specific IgE obtained 8 weeks later. Good agreement was observed in all subjects between the results of skin tests and the values for histamine and tryptase, provided that both markers were measured simultaneously. Furthermore, there was no significant difference between the concentrations of NMB-specific IgE antibodies observed at the time of the reaction and 8 weeks later. Thus anaphylaxis to neuromuscular blocking drugs can be demonstrated at the time of the reaction by measuring plasma concentrations of histamine, tryptase and specific IgE. In the event of the patient's death, such measurements may be useful in identifying the likely cause. (Br. J. Anaesth. 1992; **69**: 611–614)

KEY WORDS

Allergy: anaphylactic reactions, diagnosis, IgE antibodies. Enzymes: tryptase. Histamine. Neuromuscular relaxants.

The frequency of anaphylactic reactions during anaesthesia has been estimated at 1 in 6000 operations, with neuromuscular blocking drugs involved in 80% of cases [1]. The mechanism is mediated usually via IgE antibodies related to substituted ammonium ions [2]. The diagnosis can only be made at a later date, as skin testing must not be performed earlier than 6 weeks after the reaction [3]. However, in some cases, earlier diagnosis is important: first when surgery has been stopped but is still urgent and second for legal reasons, if the patient dies.

However, most adverse reactions occurring during anaesthesia are not anaphylactoid events [4, 5]. Thus it is important to prove *in vivo* histamine release. This can be achieved by measurement of histamine or tryptase during the reaction [6–8].

Usually, several drugs are administered during induction of anaesthesia. The role of neuromuscular blocking drugs (NMB) may be assessed by demonstrating either NMB-specific IgE antibodies or *in vitro* release of histamine [9, 10]. The latter cannot be performed soon after the reaction, because basophil histamine stores are depleted [11]. NMB-specific IgE antibodies may be detected 6 weeks after the reaction, in 87.9% of reactive subjects [12]. Recently, it has been suggested that anaphylaxis could be diagnosed in fatal cases by measuring drug-specific IgE antibodies [13]. However, to our knowledge, there has been no work to examine if such measurements are reliable at the time the reaction occurs.

Thus the goal of the study was to evaluate the accuracy of the diagnosis obtained at the time of the reaction, by measurements of plasma histamine, tryptase and NMB-specific IgE antibodies. The results were compared with those of skin tests and specific IgE antibodies measured at 8 weeks or later.

PATIENTS AND METHODS

We studied 14 patients (six male) who had adverse reactions at induction of anaesthesia. Their mean age was 46 (SD 18.3) yr (range 13–71 yr). All had received a neuromuscular blocking drug and other anaesthetic agents. The clinical signs were cutaneous, bronchopulmonary or cardiovascular. The severity of the reaction was classified according to the scale of Ring and Messmer [14] (table I).

For all the patients, NMB-specific IgE antibodies were measured immediately after the reaction and at least 8 weeks later when skin tests were performed. The mean time interval between the two sample collections was 3.9 (2.0) months (range 2–9 months). Plasma histamine concentrations were measured in all patients during the 30 min after the reaction, as recommended by Lorenz, Neugebauer and Schmal [15]. Plasma concentration of tryptase was measured in nine patients.

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TABLE I. *Comparison of the results of early investigation (plasma histamine and tryptase, and NMB-specific IgE) with those of skin tests and specific IgE obtained at least 8 weeks later in 14 patients. *According to the Ring and Messmer scale [14]. §Haemolysed sample. † Abnormal skin reactivity*

				During reaction			> 8 weeks later		
Patient No.	Sex	Age (yr)	Severity grade*	Histamine (nmol litre^{-1})	Tryptase (u litre^{-1})	IgE (%)	Skin tests	IgE (%)	Responsible drug
1	M	38	3	5250	39	4	+ve	3.5	Pancuronium
2	F	21	3	1700§	110	17.3	+ve	21.7	Suxamethonium
3	F	42	3	200	11	36	+ve	33	Vecuronium
4	F	62	3	38	11	15	+ve	12.5	Suxamethonium
5	M	66	3	45	3.3	0.7	+ve	1.1	Gelatine
6	F	37	2	17	< 2	16	+ve	14	Vecuronium
7	M	33	3	33	—	7.6	+ve	6.8	Vecuronium
8	F	71	3	5.7	8.3	2.5	+ve	1.5	Pancuronium
9	M	13	3	4	< 2	2.5	†	2.9	—
10	M	50	2	2.2	—	1	−ve	0.9	—
11	M	66	2	2.2	—	1.2	−ve	0.7	—
12	F	65	2	1.7	—	0.4	−ve	0.6	—
13	F	56	2	1.2	—	0.9	−ve	0.6	—
14	F	24	2	< 0.5	3.5	0.7	−ve	1.1	—

NMB-specific IgE antibodies [12]

A quaternary ammonium-reactive phase was obtained by linkage of choline hydrochloride to Sepharose. A first incubation step with the serum of the patient allowed binding of specific IgE to the solid phase. After washing, a second incubation step was performed with ^{125}I-anti-human-IgE IgG, followed by washing. The results were expressed as percent bound radioactivity. The within-assay coefficients of variation were 10 % for normal values and 3 % for large values. The mean value obtained in 20 control subjects was 1.3 (0.5) %. The pathological range was 5 % binding, and the intermediate range was 2.5–5 % [12]. Inhibition by neuromuscular blockers of the binding to choline was demonstrated further by incubation with the administered neuromuscular blocker.

Plasma histamine

Blood was obtained from a peripheral vein in EDTA-containing tubes and transferred immediately in chilled water to the laboratory. After centrifugation (4 °C, 800 *g*), plasma was aspirated gently without approaching the white cell layer, then frozen at −20 °C. Histamine was measured in duplicate by a competitive radioimmunoassay after akylation of histamine [16] (histamine RIA kit, Immunotech, Luminy, France). The lower detection limit of the assay is 0.2 nmol litre^{-1}. The normal mean concentration measured 15 min after anaesthetic induction in 35 control subjects was 1.63 (0.61) nmol litre^{-1}. The upper concentration for normals, calculated from mean ±3 SD (99 % confidence interval) was 3.5 nmol litre^{-1}. We have considered the pathological range as > 9 nmol litre^{-1} and the intermediate range as 3.5–9 nmol litre^{-1} (1 nmol litre^{-1} is 0.11 ng ml^{-1}).

Plasma tryptase

Mast cell concentration of tryptase was measured in duplicate in plasma or serum by an immunoradiometric assay [17] (Tryptase RIACT kit, Pharmacia, Uppsala, Sweden). The lower limit of detection of the assay is 0.5 u litre^{-1} (1 u = 1 μg of purified human lung tryptase). Eighteen of 19 anaesthetized control subjects had tryptase values < 2 u litre^{-1}. In one the tryptase concentration was 2.2 u litre^{-1}. The normal value was considered < 2 u litre^{-1} and the pathological range > 5 u litre^{-1}, according to Schwartz [6].

Skin tests

Serial dilutions of all the administered drugs were made in human serum albumin, and intradermal injections were performed as recommended by Fisher [18], 6 weeks after the reaction or later.

Statistical analysis

Data were expressed as mean (SD). Means were compared by Wilcoxon's test and linear correlation was performed using the method of least-squares. $P < 0.05$ was considered statistically significant.

RESULTS

Seven patients (Nos 1–7) had pathological concentrations of plasma histamine during the reaction (table I). Six of these seven patients had tryptase measurements made: four had increased concentrations of tryptase and two had normal or intermediate values. The seven patients had positive skin tests, six for the administered neuromuscular blocker and one (patient No. 5) for a urea-linked gelatine (Haemaccel). Five of the six patients who had reacted to a neuromuscular blocker had increased concentrations of specific IgE antibodies, the remaining one (No. 1) being in the intermediate range.

One patient had intermediate concentrations of plasma histamine and increased concentration of tryptase (No. 8). Specific IgE antibodies were not found. However, skin tests were positive for pancuronium.

The six remaining patients (Nos 9–14) had small concentrations of plasma histamine. Tryptase was measured in two: the concentration was normal or in the intermediate range. Specific IgE antibodies were

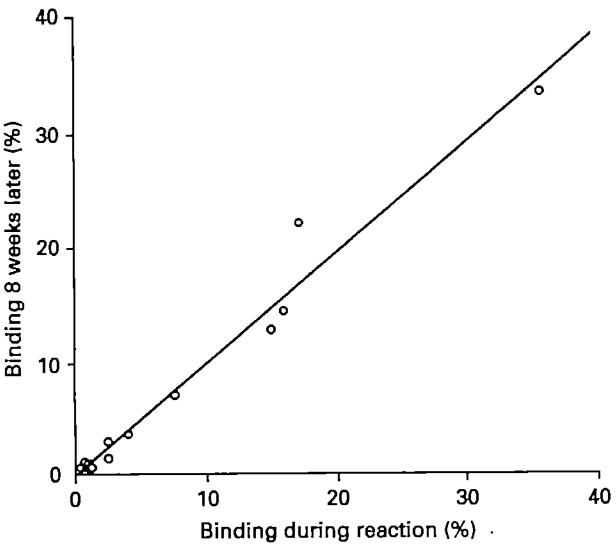

FIG. 1. Percent binding of serum IgE to quaternary ammonium-solid phase measured at the time of the anaphylactoid reaction and 8 weeks later ($n = 14$). Linear correlation ($r^2 = 0.972$; $P < 0.0001$).

found in none. Skin tests were negative for five. For the last patient (No. 9) the skin tests were not reliable because he reacted to the control solution.

The concentrations of NMB-specific IgE antibodies were compared in the 14 patients. The mean percent binding measured during the reaction was 7.6 (9.9) %, not significantly different from the mean binding ratio measured at least 8 weeks later—7.2 (9.5) %. A linear correlation ($r^2 = 0.972$; $P < 0.0001$) was found with a slope of 0.95 (0.04) and an intercept of 0.05 (0.5) (fig. 1). The values of slope and intercept were not significantly different, respectively, from 1 and 0 .

Another patient, who experienced acute bronchospasm after injection of pancuronium leading to death within 1 h, was investigated before resuscitation was stopped: plasma histamine concentration was 1120 nmol litre^{-1} and tryptase 240 u litre^{-1}. NMB-specific IgE antibody concentration was 16 %.

DISCUSSION

It has been recommended that patients undergoing anaphylactoid reactions be investigated as soon as the incident occurs [3, 9]. Plasma histamine, a major mediator involved in anaphylactic shock can now be measured routinely by a commercial radioimmunoassay of high sensitivity and specificity [16]. The half-life of histamine in plasma is in the order of minutes [19] and so the sample must be obtained as soon as possible after the reaction. Furthermore, blood basophils contain large concentrations of histamine; thus spontaneous haemolysis of the sample during blood collection may lead to false positive results because of concurrent damage of basophils. Tryptase, a stable protease stored in mast cell granules, is liberated into blood if mast cell activation occurs [6] and stays at increased concentrations in plasma for 6 h [8]. Moreover, blood cells do not contain tryptase [20], which allows for reliable measurements from haemolysed samples. Increased concentrations of these markers measured after an adverse reaction during anaesthesia suggest *in vivo* release of histamine.

In these studies, there was no discrepancy between the results of skin tests and the values of histamine and tryptase measured during the reaction. In five patients (Nos 10–14), skin tests failed to identify a responsible drug; all had moderate reactions, two having bronchospasm alone. Furthermore, plasma histamine was not increased, which suggested that *in vivo* histamine release had either occurred in very small concentrations (anaphylactoid reaction), or had not occurred. All the patients with positive skin tests had increased concentrations of plasma histamine or tryptase, or both. In patient No. 2, the sample was slightly haemolysed, but *in vivo* histamine release was confirmed by increased tryptase concentrations. In patient No. 8, histamine had disappeared from plasma, but not tryptase. In Nos 5 and 6, tryptase concentrations were not increased, but histamine concentrations were clearly pathological. Thus it is advisable to measure both histamine and tryptase from the plasma samples obtained during the reaction: if the sample has been obtained within a few minutes of the reaction, plasma histamine should be increased, but tryptase may not have reached blood yet. If blood has been sampled later, tryptase should have increased concentrations, whereas histamine concentrations may have returned to normal [8].

Neuromuscular blockers are responsible for 80 % of anaphylactic reactions during induction of anaesthesia [1], and NMB-directed IgE stay for years at increased concentrations in the serum of sensitized subjects [21]. Our results demonstrate that these IgE may be reliably measured at the time the reaction occurs, with no significant difference in the concentrations 8 weeks later. These findings suggest that increased concentrations of IgE were present before the anaphylactic event, and thus that the reaction could be anticipated, as shown for protamine [22]. The sensitivity observed in this study was 85.7 % (six patients with increased IgE of seven patients with skin tests positive to neuromuscular blockers). This value is close to the sensitivity reported previously (87.9 %) [12].

Although our results are obtained from a small number of patients, they indicate that the diagnosis of anaphylaxis to neuromuscular blockers may be obtained early, by measuring plasma concentrations of histamine and tryptase, and specific IgE antibodies during the reaction. Such measurements provide the opportunity to elucidate immediately the mechanism of the reaction: anaphylaxis, with which plasma concentrations of histamine or tryptase and of specific IgE are increased, may be differentiated from anaphylactoid response, with which specific IgE are absent, and from non-anaphylactoid reactions with which plasma histamine, tryptase and specific IgE concentrations are normal. When skin tests are not available, either because the patient cannot return to hospital or when skin reactivity is abnormal, early investigations, if performed, appear to be useful. Moreover, it is of value when forensic evidence is requested, especially if the patient dies.

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TABLE I. *Effects of various combinations of the carbon dioxide content in the gas mixture and the* $NaHCO_3$ *concentration on* P_{CO_2}, *pH and* P_{O_2} *(mean (SEM)) in the buffer solution* (n = 6)

Experimental condition	CO_2 (%)	$NaHCO_3$ (mmol litre^{-1})	P_{CO_2} (kPa)	pH	P_{O_2} (kPa)
Control	5.0	20	4.2 (0.1)	7.44 (0.01)	28.5 (1.0)
Hypocapnia	3.0	20	2.7 (0.1)	7.64 (0.05)	28.3 (0.2)
Hypocapnia, compensated pH	3.0	10	2.7 (0.1)	7.37 (0.02)	27.2 (0.3)
Hypercapnia	9.0	20	7.2 (0.2)	7.17 (0.02)	27.5 (1.2)
Hypercapnia, compensated pH	9.0	40	7.3 (0.2)	7.47 (0.00)	28.3 (0.5)

7A). The ring segments were given a tension of 1 mN mm^{-1} (length). The Krebs solution was maintained at 37°C and the contents of the baths were bubbled with gas mixtures composed of carbon dioxide, oxygen and nitrogen. Datex Normocap 102–24–02 was used to constantly monitor the gas mixture. The partial pressures of carbon dioxide and oxygen and pH in the Krebs solutions were analysed on a Radiometer ABL 300.

$PGF_{2\alpha}$ was supplied as an aqueous solution (Amoglandin, Astra, Sweden) and dilutions were made up with saline immediately before use. The composition of the Krebs solution was (mmol litre^{-1}): NaCl 119; $NaHCO_3$ 20; KCl 4.6; CaCl 1.5; NaH_2PO_4 1.2; $MgCl_2$ 1.3; glucose 11.0. Isotonic solutions containing different concentrations of K^+ were obtained by exchanging NaCl in the Krebs solution with equimolar amounts of KCl. In order to keep pH constant at different partial pressures of carbon dioxide, the $NaHCO_3$ concentration was changed from 20 mmol litre^{-1} to either 10 or 40 mmol litre^{-1}. Gas mixtures used to equilibrate the Krebs solution were composed of oxygen, nitrogen and carbon dioxide. The oxygen content was kept constant at 30 %, whereas the carbon dioxide content was varied to 3, 5 or 9 %. The combinations of $NaHCO_3$ and gas mixtures and the resulting effects on pH in the Krebs solution, are presented in table I.

After an equilibration period with 95 % oxygen and 5 % carbon dioxide, contractions were induced by K^+ 124 mmol litre^{-1} and experiments were not continued unless two reproducible contractions (±10 %) were obtained. The vessel segments were exposed subsequently to 30 % oxygen for 20 min. Control concentration–response curves [7] were obtained with either K^+ 11–124 mmol litre^{-1} or $PGF_{2\alpha}$ 2×10^{-8}–10^{-4} mol litre^{-1}. The effect of hypocapnia was studied, followed by hypercapnia. Under both conditions, pH values were allowed to vary. The effects of compensation of pH by changing the $NaHCO_3$ concentration in the buffer solutions were also studied (table I). The order of the different conditions was varied systematically. After equilibration periods of approximately 20 min, cumulative concentration–response curves were obtained through inducing contractions by a stepwise increment in either K^+ or $PGF_{2\alpha}$. In all vessel segments, the reactivity to K^+ at 95 % oxygen and 5 % carbon dioxide was verified at the end of the experiment and the preparation was discarded if this contraction deviated by more than 10 % from the initial response.

Calculations and statistical analysis

The maximum response (*E*max) in each preparation, obtained with either $PGF_{2\alpha}$ or K^+, under control conditions ($NaHCO_3$ 20 mmol litre^{-1} and 5 % carbon dioxide) was defined as 100 %. All subsequent contractions were related to this response. The control *E*max values induced by K^+ and $PGF_{2\alpha}$ were 6.7 (SEM 1.1) mN ($n = 6$) and 8.6 (1.8) mN ($n = 6$), respectively. All results are expressed as mean values (SEM), *n* denoting the number of observations (all from different patients). Estimation of the concentrations of K^+ or $PGF_{2\alpha}$ producing half maximum contraction (EC_{50}) were based on the geometrical means of the sigmoid concentration–response curves. Curve fitting was performed with Graph Pad (ISI Software, Philadelphia, Pa, U.S.A.) using the sigmoidal curve formula and assuming that the greatest measured value corresponded to *E*max. This consistently yielded correlation coefficients greater than 0.98. The Wilcoxon rank sum test was used for determination of statistical significance between groups of data. $P \leqslant 0.05$ or less was accepted as significant.

RESULTS

Variations in pH and P_{CO_2} had no effect in passively stretched arteries.

Effects on contractions induced by K^+

A decrease in P_{CO_2} (to 2.7 kPa) with a concomitant increase in pH (to 7.64) induced a small and non-significant increase in *E*max and a significant decrease in EC_{50}, whereas an increase in P_{CO_2} (to 7.2 kPa, pH 7.17), significantly depressed the *E*max and increased the EC_{50} (fig. 1A, table II). The effects of P_{CO_2} were less consistent if pH was not altered: even when a dilatator tendency at decreased P_{CO_2} (2.7 kPa) was present, this could be ascribed to a slight relative acidosis (pH 7.37) (fig. 1B, table II). Hypercapnia (P_{CO_2} = 7.3) induced no changes in either *E*max or EC_{50} (fig. 1B, table II).

Effects on contractions induced by $PGF_{2\alpha}$

Hypocapnia with uncompensated pH (P_{CO_2} = 2.7 kPa, pH 7.64), significantly increased the *E*max and EC_{50} values compared with control conditions (fig. 2A, table III). At uncompensated hypercapnia (P_{CO_2} = 7.2 kPa, pH = 7.17) the *E*max significantly attenuated and the EC_{50} value increased (fig. 2A, table III). The effects of P_{CO_2} at constant pH were even more complex. Hypocapnia (P_{CO_2} = 2.7)

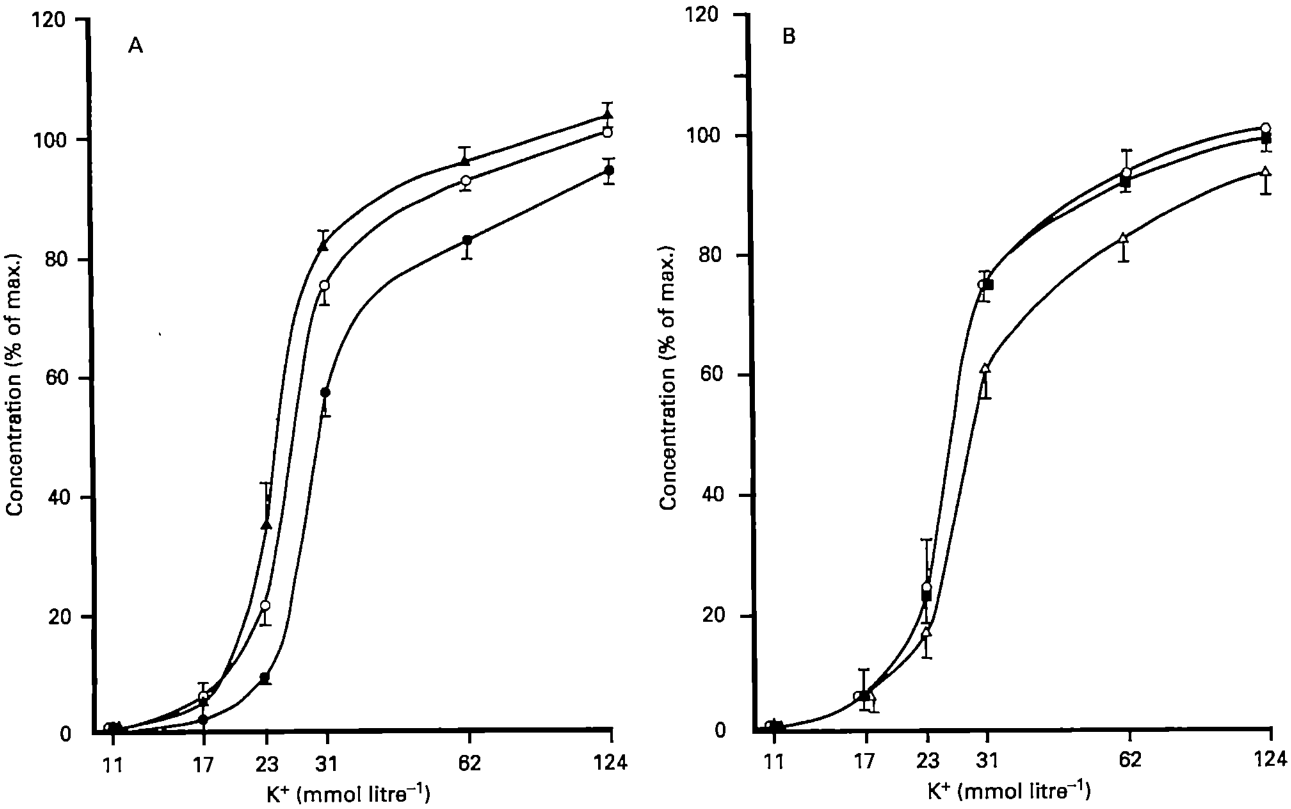

FIG. 1. Concentration–response curves (mean, SEM) obtained with K^+ ($n = 6$). A: Effects of different partial pressures of carbon dioxide: 2.7 kPa (▲), 4.2 kPa (○) and 7.2 kPa (●) with concomitant changes in pH. B: Effects of different partial pressures of carbon dioxide: 2.7 kPa (△), 4.2 kPa (○) and 7.3 kPa (■) during constant pH.

TABLE II. *Effects of carbon dioxide and pH on contractions induced by excess* K^+. *The contractions are characterized by mean* EC_{50}, *mean (SEM)* $-\log$ (EC_{50}) *and* Emax *values. Number of experiments* = 6. * $P \leq 0.05$ *compared with control*

Experimental condition	EC_{50} (mmol $litre^{-1}$)	$-\log$ (EC_{50})	*E*max (%)
Control	26.5	1.58 (0.01)	100 (0)
Hypocapnia	24.3	1.62 (0.03)*	103 (2)
Hypercapnia	29.4	1.54 (0.01)*	94 (2)*
Hypocapnia, compensated pH	28.5	1.55 (0.02)	93 (4)
Hypercapnia, compensated pH	26.5	1.58 (0.02)	98 (2)

slightly decreased the *E*max value, whereas the EC_{50} value increased (fig. 2B, table III). On the other hand, hypercapnia ($P\text{CO}_2 = 7.3$) significantly attenuated the *E*max value, whereas the EC_{50} value increased (fig. 2B, table III).

DISCUSSION

We have found that, in isolated human pial arteries, an increase in carbon dioxide tension with a concomitant change in pH diminished the vascular smooth muscle contraction. In our experimental model, $P\text{CO}_2$ was kept at 4.2 kPa during control conditions. This is the resulting $P\text{CO}_2$ in the buffer solution when the solution is bubbled with a gas mixture containing 5 % carbon dioxide which is an established procedure if bicarbonate buffered solutions are used *in vitro*. Even if this represents slight hypocapnia, which may attenuate the effect of a further reduction in $P\text{CO}_2$, the resulting findings are in accordance with previous studies, both *in vitro* on isolated cerebral arteries from cat [5] and dog [8], and *in vivo* in cat [4]. Similarly, carbon dioxide inhalation causes a marked cerebral vasodilatation in humans, whereas hypocapnia results in pronounced vasoconstriction [9, 10]. Manipulations of the extrinsic sympathetic innervation of brain vessels have little or no effect on the cerebral blood flow (CBF) response to hypercapnia [11–13], suggesting that pH, carbon dioxide, or both, may influence cerebral arteries directly. The mechanism through which these two variables modulate cerebrovascular tone has been debated. A change in arterial $P\text{CO}_2$ alters pH in blood, extracellular fluid and arterial smooth muscle cells. However, Harper and Bell [14], demonstrated that a change in intravascular pH had no influence on CBF. Instead, the effect of alterations in $P\text{CO}_2$ may be mediated by a change in perivascular pH (pH_o) [3, 4], even if a direct effect of $P\text{CO}_2$ on cerebrovascular reactivity cannot be excluded [5].

A major finding of the present study is that, while a reduction in $P\text{CO}_2$ augmented contractions induced

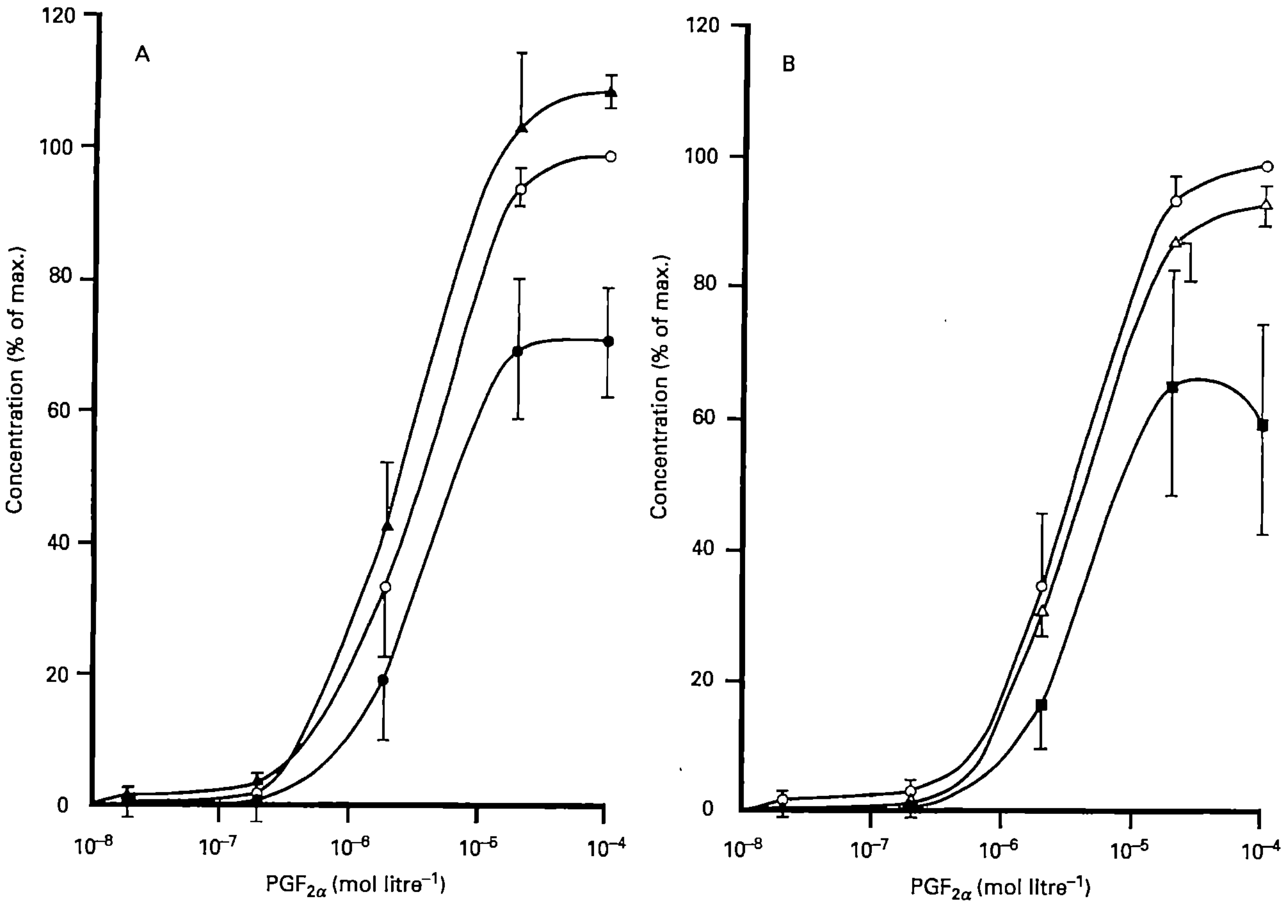

FIG. 2. Concentration–response curves (mean, SEM) obtained with PGF$_{2\alpha}$ ($n = 6$). A: Effects of different partial pressures of carbon dioxide: 2.7 kPa (▲), 4.2 kPa (○) and 7.3 kPa (■) with concomitant changes in pH. B: Effects of different partial pressures of carbon dioxide: 2.7 kPa (△), 4.2 kPa (○) and 7.3 kPa (■) during constant pH.

TABLE III. *Effects of carbon dioxide and pH on contractions induced by PGF$_{2\alpha}$. The contractions are characterized by mean EC$_{50}$ and mean (SEM) −log (EC$_{50}$) and Emax values. Number of experiments = 6.* * $P \leqslant 0.05$ *compared with control*

Experimental condition	EC$_{50}$ (mmol litre^{-1})	−log (EC$_{50}$)	*E*max (%)
Control	2.6×10^{-6}	5.59 (0.15)	100 (0)
Hypocapnia	5.1×10^{-6}	5.29 (0.20)*	110 (2)*
Hypercapnia	4.5×10^{-6}	5.35 (0.16)*	73 (9)*
Hypocapnia, compensated pH	4.1×10^{-6}	5.38 (0.12)*	92 (4)*
Hypercapnia, compensated pH	6.0×10^{-6}	5.22 (0.12)*	69 (16)*

by PGF$_{2\alpha}$, this effect was converted to a slight, but significant, attenuation when the resulting increase in pH$_0$ was prevented by adjustment of the bicarbonate concentration in the buffer solution. Similarly, a variation of PCO$_2$ had no effect on the pial arteriolar diameter in anaesthetized cats unless there was also a concomitant change in pH$_0$ [4]. Toda, Hatano and Mori [15] studied the effects of hypercapnia on helical strips of canine cerebral arteries. They found that, while compensation of pH$_0$ did restore the decreased contractility resulting from an increase in PCO$_2$, this effect was temporary and was followed by a decrease in tension to a value significantly less than control. In our experiments also, hypercapnia significantly attenuated the contractions induced by PGF$_{2\alpha}$. Compensation in pH$_0$ during hypercapnia had little effect on the mean attenuation of the *E*max value which, as our experimental method did not allow for detection of the immediate effects of increased PCO$_2$, may represent the secondary attenuation of the contractility described by these authors [15]. Direct comparison between the present results and those of Toda, Hatano and Mori [15] is difficult because of differences in both species and methodology: spiral strips [15] *vs* ring segments (present study) and a larger range of the changes in both pH and PCO$_2$ in their study as compared with ours. We have restricted the changes in PCO$_2$ to a more physiological range, which may have reduced the magnitude of the resulting effects on the contractility of the arteries; this design does, however, facilitate comparison with results obtained *in vivo*.

Decreased PCO$_2$, produced by hyperventilation, is frequently used as a means of decreasing increased intracranial pressure [2]. The mechanism behind this effect is believed to be cerebral vasoconstriction [2]. Most investigators in this area agree that the effect of hyperventilation is temporary: during prolonged periods the vasoconstriction and, hence, also the pressure reducing effect, disappears [16]. If the present *in vitro* findings and previous observations *in vivo* in cat [4] are relevant clinically, our observation that a decreased $P\text{CO}_2$ augmented contractions in human cerebral arteries only when the pH_0 was alkaline may offer an explanation for the transient effect of hyperventilation. Such a mechanism has been suggested to explain the time-dependent reversal of the vasoconstriction by hyperventilation in rabbit [17].

In contrast to our findings with $PGF_{2\alpha}$, arteries contracted by K^+ failed to respond to changes in $P\text{CO}_2$ when pH was compensated. The variability in the effects of $P\text{CO}_2$ and pH_0 on contractions induced by different agents may at first seem difficult to explain. However, it has been suggested that an increased $P\text{CO}_2$ may attenuate contractions by hyperpolarization of the cell membrane [18]—an effect which would be counteracted during maximal depolarization with K^+. However, it is not possible to induce relaxant effects by hyperpolarization in this state, as the enzyme (Na–K-ATPase) mediating hyperpolarization is already maximally activated [19]. Furthermore, H^+ ions may have an inhibitory effect on smooth muscle contractility, via several possible mechanisms: reduction in calcium influx [20–22], inhibitory effect on the myofilaments [23–25], stimulation of intracellular sequestration of calcium [26], decreased release of calcium from the sarcoplasmic reticulum [25, 27] and changes in the receptors in the cell membrane [28–30]. Our finding that increased and decreased $P\text{CO}_2$ caused a rightward shift of the concentration–response curves (increased EC_{50} values) obtained with $PGF_{2\alpha}$ suggests a decrease in receptor affinity which may reflect changes in the receptor protein. As K^+-induced contractions do not involve interactions on specific receptors or release of intracellularly sequestered calcium [31], the latter mechanisms are less likely to mediate the effect of pH_0 under such conditions. This may offer an alternative explanation for some of the variations in the effects of $P\text{CO}_2$ depending on the mechanism of activation of the arteries. Thus the variation in the effects of $P\text{CO}_2$ on arteries contracted with K^+ or $PGF_{2\alpha}$ is not surprising.

Changes in $P\text{CO}_2$ at constant pH had no significant effects on arteries contracted by excess K^+. This contrasts with the finding in isolated cerebral arteries of the dog [15], that the contractile effect of K^+ 20 mmol litre^{-1} was attenuated during an almost three-fold increase in $P\text{CO}_2$, an effect that could be counteracted only partially by maintaining a constant pH_0. However, the variation in $P\text{CO}_2$ was less in our study than in the study by Toda, Harano and Mori [15]. In dog coronary arteries, Rinaldi and co-workers [32] demonstrated that the effect of pH_0 on contractions was independent of changes in $P\text{CO}_2$. Such divergent results may be explained by differences in species, size and origin of the vessels, and experimental conditions. Thus it is difficult to extrapolate results either from animal experiments to the human situation or from peripheral to cerebral arteries.

In conclusion, the present study has demonstrated that hypocapnia increased contractility in human pial arteries, whereas hypercapnia had the opposite effect. However, the enhanced contractile state produced by decreasing $P\text{CO}_2$ was not observed when pH was maintained constant.

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REVIEW ARTICLE

MASSIVE BLOOD TRANSFUSION

M. D. J. DONALDSON, M. J. SEAMAN AND G. R. PARK

Massive blood transfusion may be defined either as the acute administration of more than 1.5 times the patient's estimated blood volume [36], or as the replacement of the patient's total blood volume by stored homologous bank blood in less than 24 h [18]. The purpose of this review is to provide the reader with a practical approach to the initial management of the acutely bleeding, hypovolaemic patient, together with a description of some of the newer agents and techniques now available to treat major haemorrhage.

Acute haemorrhage leading to acute hypovolaemic shock is a medical emergency carrying a high mortality and therefore requires prompt and effective treatment. Initial management includes rapid restoration of the circulating blood volume, correction and maintenance of adequate haemostasis, oxygen delivery and colloid osmotic pressure and correction of any biochemical abnormalities. The investigation and treatment of the underlying cause of bleeding should also be undertaken as soon as possible (table I).

In addition to blood loss, hypotension may result from other coexisting causes that require treatment. These include decreased ionized calcium concentration, development of arrhythmias, pre-existing cardiac disease, sepsis (causing vasodilatation), air embolism, hypothermia and immunological reaction to drugs.

RESTORATION AND MAINTENANCE OF CIRCULATING BLOOD VOLUME

The rapid and effective restoration of an adequate circulating blood volume (so that tissue perfusion and oxygen delivery are maintained) is crucial in the early management of major haemorrhage, as mortality increases with increasing duration and severity of shock.

Venous access and monitoring

Poiseuille's equation states that, for a Newtonian fluid under conditions of laminar flow, the resistance to flow is directly proportional to the length of the tube, the viscosity of the fluid and the pressure gradient, and inversely proportional to the fourth power of the radius. Under these conditions, doubling the radius increases the flow by a factor of 16, while shortening the length of cannula or reducing the viscosity of fluid has considerably less effect.

In the acutely hypovolaemic patient, at least two large-gauge i.v. cannulae should be inserted into appropriately sized veins, usually in the antecubital fossae. If peripheral venous access is difficult, a cannula may be inserted into a large, central vein such as the subclavian, internal jugular or femoral vein. Alternatively, a venous cutdown may be performed on the saphenous vein at the ankle.

When a massive transfusion is anticipated during surgery, at least two large-gauge venous cannulae (12-gauge) should be inserted, solely for transfusion purposes. In addition, an arterial cannula and triple lumen central venous cathether may prove useful, allowing rapid blood sampling and direct measurement of arterial and central venous pressures, respectively. The triple lumen catheter also provides access for intermittent bolus administration of drugs, or drug infusions. Alternatively (or in addition), a sheath introducer (8-French gauge) may be inserted into a central vein, so providing a large cannula for transfusion and a means whereby a pulmonary artery catheter can be inserted, when indicated.

Unless contraindicated by pelvic or urethral injury, a urethral catheter should be passed and urine output monitored hourly. In addition, central and peripheral temperatures should be recorded and pulse oximetry used (fig. 1).

Needles and sharp objects should be handled and disposed of carefully to avoid needlestick injury. The wearing of gloves is recommended to prevent contamination of the hands with spilled blood. The use of three-way taps (with or without extension

TABLE I. *Management priorities in massive transfusion (the exact priority depends upon the circumstances)*

Restore circulating blood volume
Maintain oxygenation
Correct coagulopathy
Maintain body temperature
Correct biochemical abnormalities
Prevent pulmonary and other organ dysfunction
Treat underlying cause of haemorrhage

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KEY WORDS
Blood. Transfusion.

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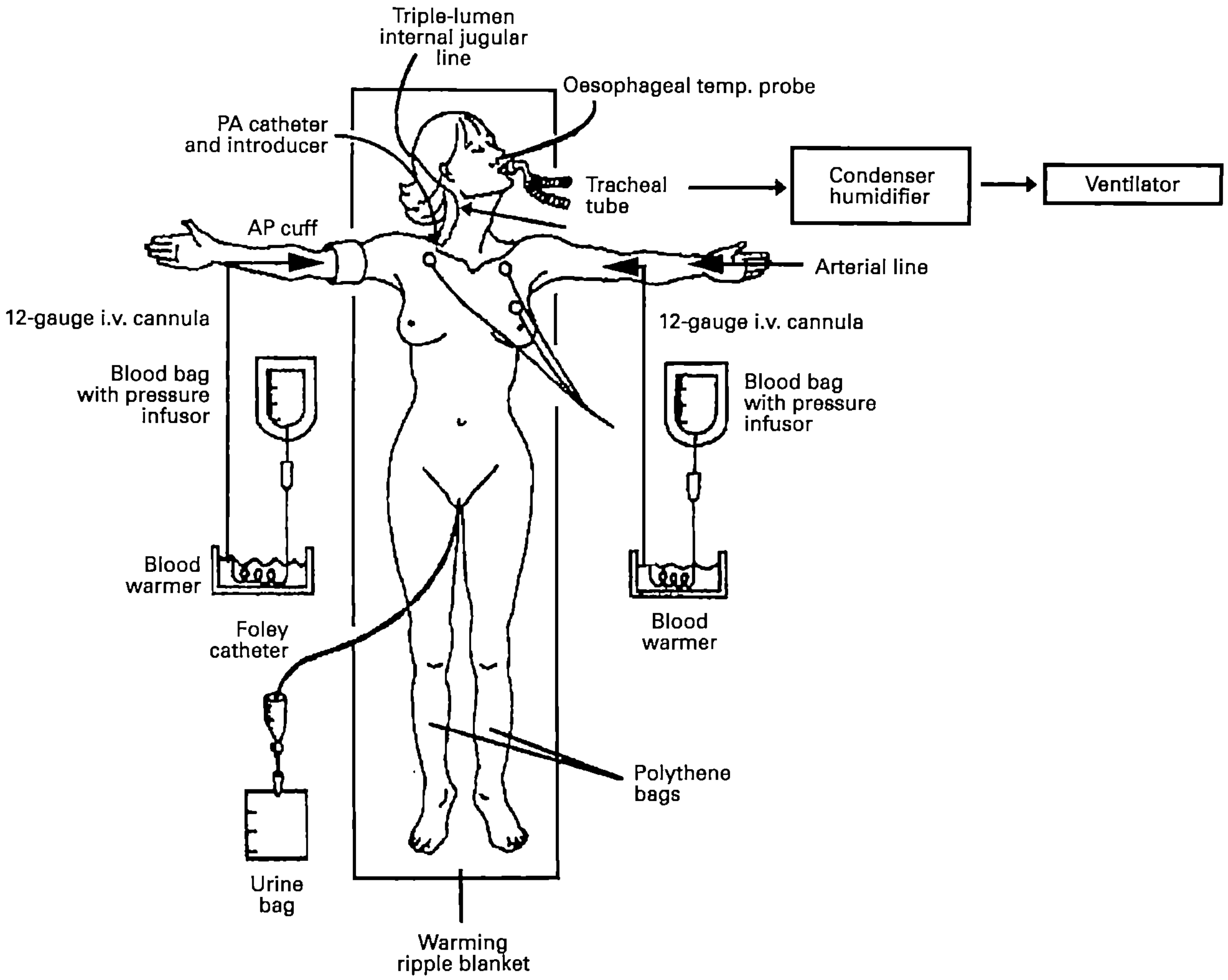

FIG. 1. Position of monitoring and replacement systems in a patient expected to require massive blood transfusion.

tubing) reduces the need to use needles for drug administration or blood sampling.

Initial resuscitation: crystalloid or colloid?

The success of initial resuscitation in the acutely hypovolaemic patient depends more upon speed and adequacy of repletion than upon which fluids are used, anaemia being tolerated better than hypovolaemia. However, the debate continues as to which is the best fluid for this initial resuscitation [11,12,19,31,40] and there have been no adequate controlled clinical trials comparing the outcomes in patients resuscitated either with albumim or with other colloid solutions (gelatins, dextrans or hydroxyethyl starch). Two facts are, however, not in dispute. First, about 50–75% less colloid than crystalloid is required to achieve a given end-point in blood volume expansion, but at an increased financial cost. The need to give more fluid when using crystalloids may increase the logistic difficulties of early resuscitation and result in greater thermal stress if the fluids are cold. Second, unlike crystalloids, colloids are associated with allergic reactions, albeit rarely.

In the majority of studies, the type of fluid administered did not influence outcome. It is not known, however, if there are any identifiable subgroups of patients in whom the choice of replacement fluid is important. Several such groups have been suggested including the elderly, those with low colloid osmotic pressures and poor wound healing, patients suffering from anaphylactic shock and those with non-cardiogenic pulmonary oedema. In practice, however, combined therapy using both crystalloids and colloids is often used and has been shown to produce better results in experimental shock models than the use of either colloid or crystalloid alone [45].

Colloid solutions decrease the concentration of clotting factors by haemodilution, but both hydroxyethylstarch and dextran reduce factor VIII concentration to a greater extent and both are incorporated into polymerizing fibrin fibres, resulting in large, bulky clots and enhanced fibrinolysis [48]. However, the degree to which the circulating blood volume can be replaced by plasma substitutes depends more upon the dilution of the cellular components of the blood than on its plasma components. Although somewhat arbitrary, a haemoglobin concentration of approximately 10 g dl^{-1} (or a PCV of 30–35%) represents the threshold below which oxygen delivery is likely to be insufficient even when a large circulating blood volume and cardiac output are maintained. However, it is difficult to define specific concentrations below which transfusion of red cells becomes mandatory, and these values may be grossly misleading after acute haem-

TABLE II. *Baseline laboratory investigations in acute haemorrhage*

Blood transfusion (10 ml clotted blood)	Group Antibody screen Compatibility testing
Haematology (2 ml in EDTA)	Haemoglobin PCV Platelet count
Coagulation (5 ml in citrate)	Clotting screen
Biochemistry (5 ml in lithium heparin)	Urea and electrolytes

orrhage because they may not reflect the degree of blood loss for some hours.

Measurement of blood loss

During surgery, blood loss is traditionally estimated by weighing swabs and measurement of blood aspirated into the suction apparatus. In massive haemorrhage, the value of these methods is questionable, as a considerable amount of blood is inevitably spilled onto the drapes, floor and surgeons. In traumatized patients, further large loss of blood may also have occurred before arrival in hospital, or may be concealed in the limbs and pelvis at the site of fractures, or in the chest or abdomen. All this can result in an underestimate of the true blood loss, with consequent inadequate replacement. Rather than rely on these poor estimates of blood loss, patients should be transfused according to measured cardiovascular variables such as heart rate, arterial pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac output, oxygen delivery and oxygen consumption. The measurement of PCV and blood lactate concentrations may also be helpful.

Blood selection and crossmatching

At the first opportunity, blood samples should be sent urgently to the laboratory (table II), together with a warning of the urgent need for blood for transfusion. When unexpected major haemorrhage occurs and blood is required rapidly, uncrossmatched blood may be requested urgently (assuming the patient's blood group is known and the presence of atypical antibodies has been excluded). Then, compatibility testing simply involves checking the ABO and D group of the units before transfusion. However, in cases where the blood group of the patient is not known, O Rhesus Negative blood may be infused initially, before changing to ABO-specific blood when the patient's blood group has been identified.

If atypical antibodies are known to be present and major haemorrhage is anticipated, sufficient antigen-negative blood should be crossmatched in advance and reserved. However, if large supplies of antigen-negative blood are not readily available, it may be necessary to use only ABO-compatible blood during the massive transfusion period. The antigen-negative blood should then be given when the rate of blood loss has been substantially reduced.

An accurate record should be kept of the amount of blood and fluid given, including each unit number and blood group, as any transfusion reaction or transfusion-related infection requires identification and retrieval of the units responsible. In our experience, immunologically-mediated reactions to blood or blood products are rare. The reasons for this are not clear, but may be a result of the small concentrations of circulating antibodies and inflammatory mediators owing to their dilution. Nevertheless, ABO-incompatible haemolytic transfusion reactions are the most common cause of acute fatalities because of blood transfusion, and are likely to occur in the emergency setting because of clerical errors [20]. In addition, a haemolytic reaction may easily be overlooked in a critically ill patient or attributed mistakenly to other causes.

As there is often a conflict in priorities for the doctor's attention in these circumstances, the task of checking and recording the fluids administered may be delegated to other theatre personnel or assistants. It is our normal practice for two people to check all blood when it first arrives in the operating theatre.

Pressure bags, blood warming and rapid infusion devices

The requirements of a transfusion system for the management of major haemorrhage include the ability to transfuse blood at fast flow rates (up to 500 ml min^{-1}) and at temperatures greater than 35 °C. One such system uses a constant pressure infusion device [23] combined with an efficient blood warmer (Grant B12) and a purpose-designed double-length blood-warming coil [46]. Efficient counter-current aluminium heat exchangers have been investigated under conditions of a high flow and found to be effective [4]. Priming or flushing blood through the system with fluids containing calcium (such as compound sodium lactate and Haemaccel) should be avoided, as this may result in blood clot formation in the tubing [3]. This results from the reversal, by calcium ions, of the anticoagulant effect of citrate. The gas bubbles seen in the warming coil when a blood warmer is in use result from release of dissolved carbon dioxide from the blood during warming, and usually are of no clinical significance.

The Haemonetics Rapid Infuser device (fig. 2) has a 3-litre reservoir into which cell-saved (see below) or banked blood and fresh frozen plasma can be stored, warmed and infused at rates of up to 2 litre min^{-1} [42]. The system also incorporates a 40-μm high-flow blood filter, pressure sensor, air detector and heat exchanger, and can be prepared for use in about 3 min.

If such equipment for rapid transfusion is not available or cannot be used (i.e. with fluid stored in glass bottles), the speed of transfusion can be increased by simple manoeuvres. For example, increasing the height of the fluid above the patient or using intermittent manual compression of the lower chamber of the giving set when full of fluid (in such a way that the ball valve seals off the top inlet channel) are two such methods. Alternatively, using a large syringe and a three-way tap in line, fluid can

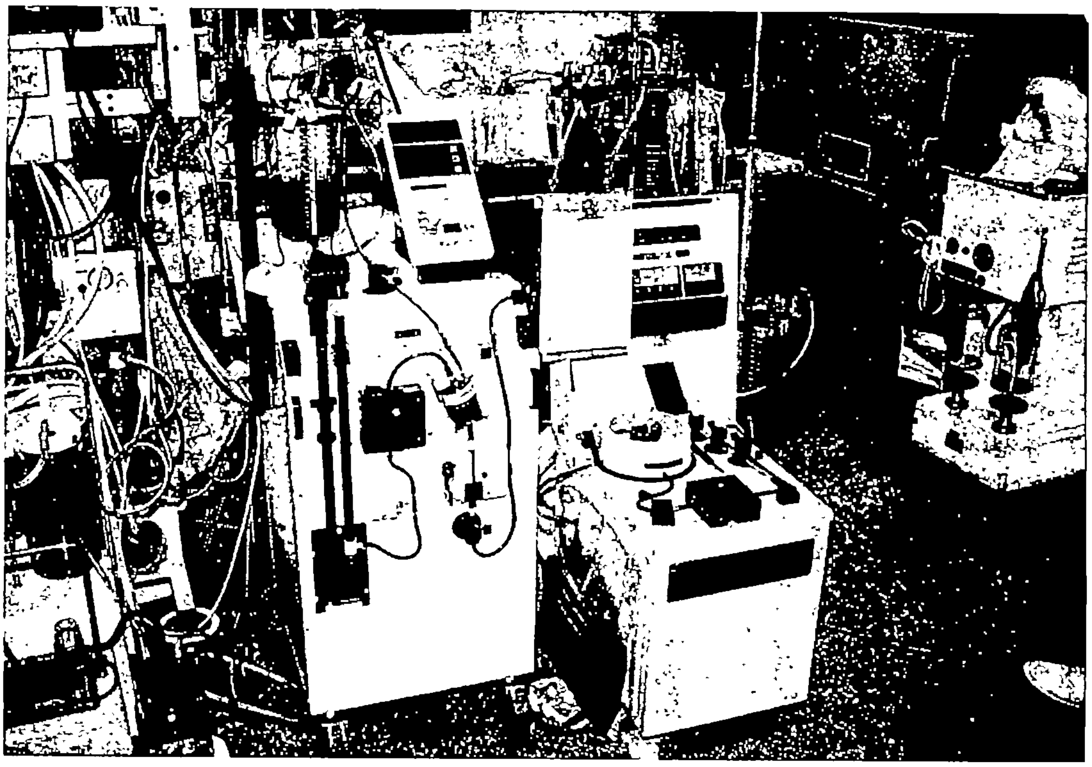

FIG. 2. The Haemonetics Rapid Infuser Device (left) and Cell Saver (right).

be drawn rapidly into the syringe from the giving set, before being administered to the patient through the three-way tap. Although no longer widely available, a manually operated Martin's rotary pump may be used. Its major disadvantage is that it tends to pull the administration set out of the infusion bag.

Intraoperative autotransfusion

Autotransfusion or autologous transfusion can be defined as the reinfusion of blood or blood products derived from the patient's own circulation. The main advantage of autotransfusion is that it avoids the complications associated with homologous transfusion, which include infection, febrile reactions, anaphylaxis, haemolytic transfusion reactions and immunosuppression. In addition, autologous blood may be the only option for some patients, especially those with rare blood phenotypes or those with rapid blood loss. It may also be acceptable to some patients on religious grounds who refuse transfusion of homologous blood. Autologous transfusion should also reduce the workload and conserve stocks in blood banks [28,47].

Blood for reinfusion may be obtained from the patient either by preoperative donation or during operation by a process of blood salvage. Preoperative donation, involving either predeposit programmes or preoperative haemodilution, is an elective procedure and is not, therefore, of benefit in the management of unexpected major haemorrhage.

Intraoperative autotransfusion using an automated cell saver system such as the Haemonetics Cell Saver 4 (fig. 2) is of great value in decreasing the transfusion requirement for bank blood when a large blood loss occurs [9]. In addition, the blood is compatible, has normal red cell concentrations of 2,3-diphosphoglycerate, is already warm and is available quickly. During autologous transfusion with the Haemonetics system, blood aspirated from the surgical field is collected via double-lumen suction lines where it is mixed with anticoagulant solution (heparinized saline) and transferred to a reservoir. The blood is filtered, centrifuged and washed with saline before resuspension in saline and transfer to a reinfusion bag at a PCV of about 50%. The discarded supernatant solution contains debris from the surgical field, white blood cells, platelets, activated clotting factors, free plasma haemoglobin and anticoagulant. Three units of blood can automatically be processed in approximately 10 min, and the cell saver can be used in conjunction with the rapid infusor device (fig. 2) to supplement homologous transfusion if large blood losses are expected [Smith MF, unpublished observations].

However, although the disposable plastic software can be assembled quickly, technical help must be available in the operating theatre if the cell saver is to be used safely and efficiently. To minimize the infection risk, the time elapsing between the start of collection and reinfusion should not exceed 12 h. Relative contraindications to the use of the cell saver include blood contamination by bacteria, intestinal contents or tumour cells [8].

An alternative manual method of intraoperative blood salvage is the Solcotrans Autologous Collection System, although its capacity is limited. Blood is drained or sucked through a 40-μm blood filter into a specially designed reservoir containing acid citrate glucose; the anticoagulated whole blood is then reinfused.

Potential complications of blood salvage systems include haemolysis, coagulopathy resulting from infusion of residual anticoagulant and dilution of coagulation factors and platelets, hypocalcaemia (when citrate is used) and air embolism.

COAGULATION CHANGES

Aetiology

In situations other than those of liver transplantation and in patients with a pre-existing coagulopathy, it is unusual for a significant reduction of plasma coagulation factors to occur solely as a result of massive transfusion of stored whole blood [7,37]. Stored whole blood contains adequate amounts of coagulation factors I, II, VII, IX, X, XI and XII.

Concentrations of factors V and VIII are reduced in stored blood, although these may be adequate for haemostasis [39] (the critical concentration of factor VIII is generally considered to be 35% of the normal plasma concentration). Furthermore, factor VIII is an acute phase protein and the stress of surgery and trauma increases its rate of production. Nevertheless, dilutional coagulopathy can be expected when replacement therapy has largely consisted of fluid containing no coagulation factors, red cell concentrates or red cells suspended in additive solutions. Therefore, after the first 4 u of a massive transfusion, it is advisable to use whole blood (preferably less than 7 days old) in order to maintain haemostasis and colloid osmotic pressure and so reduce the requirement for fresh frozen plasma (FFP). Whole blood that has been stored for 2 or 3 days is devoid of functioning platelets, although some have suggested that significant platelet function persists for longer than this [32]. A massive transfusion leads to a decrease in platelet count, but not to the concentrations predicted by the washout curve in a blood exchange model [7,37]. There seems to be a considerable reserve of platelets which can be synthesized or released rapidly from the spleen and marrow into the circulation when required.

The diffuse pathological bleeding that sometimes develops in patients receiving a massive transfusion is not therefore caused primarily by dilutional effects, but probably has many causes (table III). Clinically, microvascular bleeding produces oozing from the mucosae, raw wounds and puncture sites, together with generalized petechiae and an increase in size of contusions. Disseminated intravascular coagulopathy (DIC), leading to thrombocytopenia and a reduction of plasma coagulation factors, may also occur in up to 30% of patients during a massive transfusion [34]. It is a complication of shock and inadequate or delayed resuscitation (leading to hypoperfusion) or of the surgery itself (with release of tissue thromboplastin). Physiological changes such as the development of metabolic acidosis, hypothermia, hypocalcaemia and hypokalaemia exert adverse effects on coagulation which improve when they are corrected. In summary, it is primarily the disease itself (hypoperfusion) and not the treatment (transfusion) that causes the coagulopathy in these patients [7,27,37].

TABLE III. *Causes of coagulopathy after massive blood transfusion*

Pre-existing defects, caused by the underlying disease or drugs used
Dilution by replacement therapy
Artificial plasma expanders, e.g. dextran and hydroxyethyl starch
Stress
Tissue injury
Shock
Bacteraemia

In patients with severe liver disease, the pre-existing coagulopathy consists typically of a decrease in platelet count (caused by hypersplenism and a decreased platelet survival time) and in all coagulation factors except factor I and V (because of a decrease in the synthetic ability of the liver). These deficiencies lead to a prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT). If the coagulopathy is severe it may require correction with platelets and fresh frozen plasma in the period immediately before operation to facilitate safe insertion of intravascular monitoring catheters and to reduce bleeding during the operation.

Platelet dysfunction is the major haemostatic defect in patients with uraemia. They may benefit from treatment with desmopressin (see below), as will patients with haemophilia A and von Willebrand's disease.

Monitoring of coagulation and replacement therapy

In the past, standardized guidelines for the administration of platelet concentrate (PC) and fresh frozen plasma (FFP) have been used. These included the administration of FFP 2 u for each 10 u of blood transfused and PC 6 u for every 20 u of blood [13]. However, there are no controlled studies showing a clinical benefit from these regimens and they carry an increased infection risk associated with pooled blood component administration, together with an increased cost. Therefore the need for FFP, PC and specific coagulation factors should, whenever possible, be established by laboratory evidence of a deficiency (table IV).

While delays in acquiring the results of laboratory tests pose a formidable problem, coagulation can be monitored in the operating theatre using an *in vitro* determination of whole blood clotting time, such as the Hemochron System. This measures the activated clotting time [16,43] and was designed primarily for monitoring heparin therapy. It is less sensitive and less specific in diagnosing plasma coagulation factor deficiencies than the PT or the APTT. However, rapid estimation of the trends in PT and APTT can now be obtained in theatre using the Ciba Corning 512 coagulation systems [Luddington RL, Smith MF, unpublished observations]. Others have demon-

TABLE IV. *Basic screening tests for bleeding after operation*

Platelet count
Prothrombin time
Activated partial thromboplastin time
Plasma fibrinogen concentration
Fibrinogen degradation products, when indicated

strated the diagnostic value of thrombelastography in operations such as liver transplantation [26].

An increase in the PT and APTT to more than 1.5 times the upper limit of normal correlates with clinical coagulopathy and justifies the use of FFP, providing a coagulopathy is evident clinically. FFP should then be given rapidly and in adequate quantities, 4 u (800 ml) being the usual amount for an adult. The role of platelet counts in the management of massive transfusion remains controversial. Confirmation of thrombocytopenia (platelets $< 50 \times 10^9$ litre^{-1}) should probably be sought in addition to clinical evidence of microvascular bleeding, before the administration of platelets. A standard adult dose is PC 6–8 u (concentrate 1 u/10 kg body weight). Ideally, ABO and Rhesus-specific PC should be used and given preferably via a platelet administration set, although a standard blood administration set suffices.

Laboratory tests of coagulation are useful in the diagnosis of abnormal haemostasis and in directing therapy and monitoring its effects, but used alone cannot determine the need for transfusion of PC or FFP. Marked abnormalities in laboratory tests may be present without clinically abnormal bleeding and, in these situations, PC and FFP should be withheld until the coagulopathy becomes clinically evident, unless substantial blood loss is expected to continue [14]. Conversely, when inadequate coagulation is clinically evident, the need to transfuse PC or FFP may precede the availability of laboratory confirmation. However, there is no place for the prophylactic use of PC or FFP in massive transfusions.

The diagnosis of disseminated intravascular coagulation (DIC) can be made usually by establishing substantial increases in PT, APTT and fibrinogen degradation products (FDP), together with a markedly decreased platelet count and fibrinogen concentration. During large transfusions, the distinction between DIC and dilutional coagulopathy hinges upon the demonstration of an increased concentration of FDP and the finding that laboratory abnormalities are disproportionately greater than those expected from haemodilution alone. In general, the best treatment of DIC is to remove the cause but, once established, FFP, PC and cryoprecipitate (as a source of fibrinogen) are often needed.

"Fresh" whole blood, although theoretically useful in preventing or treating a coagulopathy, is rarely available because of the time needed for collection, grouping, compatibility testing, microbiological screening and transport. In practice, it has no advantage over the use of stored whole blood or red cell components combined with FFP and PC.

Adjunctive techniques and pharmacological therapy

A variety of techniques have been used in certain circumstances to control bleeding temporarily. These include packing of body cavities, the placement of a Sengstaken–Blakemore tube and the use of medical antishock trousers [41].

Additional drug therapy may also be beneficial in the bleeding patient in some situations. For example, desmopressin ([1-deamino, 8-D-arginine] vasopressin) is a synthetic analogue of vasopressin and alters coagulation by its effects on circulatory endothelial cells and platelets. It may prove useful in patients with Haemophilia A, von Willebrand's disease and uraemia [21]. Potential complications resulting from its use include a decrease in free water clearance, hypotension or hypertension, and thrombosis.

Antifibrinolytic agents (such as tranexamic acid) bind to plasminogen and plasmin and interfere with their ability to split fibrinogen. Patients with normal haemostatic function who bleed excessively after prostatic surgery (by release of tissue plasminogen activator from prostatic tissue) may benefit from antifibrinolytic therapy. Cardiopulmonary bypass is commonly accompanied by fibrinolysis, and antifibrinolytic therapy appears to decrease bleeding without increased risk after cardiac surgery [22]. The anhepatic phase of liver transplantation is similarly associated with increased fibrinolytic activity, and antifibrinolytic therapy has been shown to be beneficial in these patients [25]. Potentially undesirable effects of these agents include increased risk of systemic thrombosis, and patients with bleeding in the kidneys or ureters may fill the upper urinary tract with thrombus. DIC is also a contraindication to antifibrinolytic therapy.

Aprotinin (Trasylol) is a serine protease inhibitor which has been shown to decrease blood loss during cardiac surgery [2] and liver transplantation [33, 38], although its mechanism of action in these situations remains unknown. Allergic reactions and renal toxicity arouse concern about its clinical safety.

CORRECTION OR PREVENTION OF BIOCHEMICAL ABNORMALITIES

Citrate toxicity and decrease in ionized calcium

Each unit of blood contains approximately 3 g of citrate as anticoagulant. In normal circumstances, this is metabolized rapidly by the liver, and transfusion rates of blood in excess of 1 u every 5 min or liver function must be impaired before citrate metabolism becomes overwhelmed. Bunker, Bendixen and Murphy [5] infused sodium citrate into six anaesthetized humans and nine anaesthetized dogs. At the plasma concentrations of citrate they observed (which were similar to those during massive blood transfusion in both dogs and humans: 2–4 mmol litre^{-1}), both cardiac output and arterial pressure decreased by up to 40% because of myocardial depression.

The decrease in myocardial function is caused by citrate binding to the ionized calcium fraction in blood. This reduces the amount available for the normal physiological actions of calcium. The clinical manifestations of citrate intoxication are those of hypocalcaemia: hypotension, small pulse pressure and increased diastolic and central venous pressures. However, transient changes in ionized calcium concentrations cause little haemodynamic disturbance and the routine use of calcium with blood transfusion is not recommended unless hepatic function is compromised. This may be caused by a low cardiac output, hypothermia, liver disease or liver transplantation and in these situations, the chance of developing a decreased calcium concentration and citrate toxicity is increased.

Calcium also plays an essential part in both the extrinsic and intrinsic coagulation pathways. A bleeding diathesis associated with hypocalcaemia is uncommon, as cardiac arrest is said to occur before the plasma concentration decreases to a value that affects coagulation [35]. Other authors, however, have reported interference with coagulation before cardiac arrest [26].

The adverse effects of hypocalcaemia can be treated, either empirically by administration of calcium chloride if the patient becomes hypotensive and is not hypovolaemic, or on the basis of a measured decreased plasma concentration of ionized calcium [24]. Although it has been suggested that calcium gluconate is less effective than calcium chloride because it must be metabolized, this has not been proven and if equimolar quantities of each are given, no difference can be demonstrated [17]. We routinely treat hypocalcaemia with 13.4% calcium chloride containing calcium 0.912 mmol ml^{-1} rather than the weaker 10% calcium gluconate solution which contains only 0.22 mmol ml^{-1} of calcium.

The effects of blood transfusion on the plasma concentrations of citrate and calcium during liver transplantation have been studied [15]. During the dissection phase, plasma citrate concentration (normal range 0.08–0.12 mmol $litre^{-1}$) increased from the mean preoperative value of 0.09 mmol $litre^{-1}$ to 1.57 mmol $litre^{-1}$ as blood was transfused. However, during the anhepatic period when citrate metabolism did not occur, plasma citrate concentrations increased further, reaching a maximum of 3.2 mmol $litre^{-1}$. When the donor liver was revascularized, and metabolism of citrate was resumed, the plasma concentration decreased to 1.17 mmol $litre^{-1}$. Concentrations of ionized calcium decreased to 0.68 mmol $litre^{-1}$ (normal range 1.18–1.29 mmol $litre^{-1}$) as citrate concentrations increased.

Potassium

The potassium concentration in stored blood increases to approximately 30 mmol $litre^{-1}$ after 3 weeks of storage. After transfusion, viable red blood cells re-establish their ionic pumping mechanism and intracellular reuptake of potassium occurs [50]. While transient hyperkalaemia has been observed during massive transfusions and correlates strongly with the rate of transfusion [30], more commonly hypokalaemia is observed [54]. It follows that electrocardiographic monitoring is advisable during massive blood transfusions.

Acid–base disturbances

Three-week-old stored citrated blood contains an acid load of up to 30–40 mmol $litre^{-1}$ and this originates mainly from the citric acid of the anticoagulant and the lactic acid generated by red cells during storage. Both of these organic acids are normal intermediary metabolites and usually are metabolized rapidly. Citrate is metabolized to bicarbonate and may produce a profound metabolic alkalosis after transfusion. Because of this, it is not usually necessary to correct minor degrees of metabolic acidosis. The impact of transfusion of stored blood on the acid–base status of the recipient is complex, and depends upon the rate of administration, rate of citrate metabolism and the changing state of peripheral perfusion of the recipient, with shocked patients being more likely to develop a metabolic acidosis.

OTHER COMPLICATIONS OF BLOOD TRANSFUSION

Hypothermia

The problems attributable to hypothermia include reduction in citrate and lactate metabolism (thereby increasing the probability that the patient will develop hypocalcaemia and a metabolic acidosis during transfusion), an increase in the affinity of haemoglobin for oxygen, impairment of red cell deformability, platelet dysfunction and bleeding [52] and an increased tendency to cardiac arrhythmias [6]. Core temperature measurement is therefore important during massive blood transfusion and can be measured with a temperature probe at the midpoint of the oesophagus. Some workers use an oesophageal temperature probe with a stethoscope to permit monitoring of breath sounds and this is particularly useful in children. If a pulmonary artery catheter is being used, then pulmonary artery temperature can be measured in place of an oesophageal temperature probe.

Body temperature may decrease because of administration of large volumes of cold fluids and blood (which is stored at 4 °C) or because of the loss of radiant heat and latent heat of evaporation of body fluids from the open abdominal or thoracic cavity or skin (especially in burned patients). Furthermore, if ventilatory gases are not warmed adequately and humidified during operations of long duration, this contributes to heat loss; this may be prevented by the use of a heat and moisture exchanger [44].

This decrease in body temperature may be minimized by placing the patient on a heated "ripple" mattress and by warming all i.v. fluids. The patient may also be wrapped or covered in thermally insulating plastic drapes [46]. In small children an overhead infra-red heater minimizes heat loss from radiation, although this may make surgical access difficult. Alternatively, the ambient temperature of the theatre may be increased.

Pulmonary dysfunction

Although controversial, pulmonary dysfunction after transfusion is thought to be caused or exacerbated by the formation and subsequent administration of microaggregates formed in stored blood. The presence and composition of these microaggregates in stored blood was first reported in 1961 [49]. They are composed largely of degenerating platelets, granulocytes, denatured proteins, fibrin strands and other debris, and their rate of formation and size (10–200 μm in diameter) vary according to the different types of storage solution. Complications that have been associated with micro-

TABLE V. *Changes observed in a 6.7-kg child undergoing orthotopic liver transplantation (estimated blood volume 0.53 litre)*

	Start	Clamps on	Clamps off	End
Time	19:30	23:30	00:20	02:00
Blood loss (ml)	20	5430	7680	9096
Ionized calcium (mmol litre^{-1})	1.1	0.79	0.91	1.95
Calcium chloride (mmol given)	0	50	56	58
Potassium (mmol litre^{-1})	4.2	7.5	3.2	2.2
Urine (ml)	0	52	138	358
Temperature (°C)	38.5	36.6	35.3	35.5
Sodium (mmol litre^{-1})	130	144	150	154
Activated clotting time (s)	177	175	162	165

aggregate formation and subsequent transfusion include non-haemolytic febrile reactions, pulmonary injury, thrombocytopenia, fibronectin depletion and histamine release. However, because of conflicting findings in both experimental and clinical studies, controversy continues to surround the extent to which microaggregates in stored blood contribute to the production of post-transfusion pulmonary dysfunction [10]. The combination of shock, sepsis, tissue injury and massive transfusion often culminates in the adult respiratory distress syndrome.

Blood filters, designed to remove these aggregates, are of two types: depth filters which remove particles by impaction and adsorption, and screen filters which operate on a direct interception principle and have an absolute pore size rating (usually about 40 μm). A standard blood administration set contains a filter of 170 μm.

Problems which have been associated with the use of microfilters include increase in resistance to flow as the filter becomes blocked, haemolysis, platelet depletion of donor blood and complement activation. With practice, the filter usually takes less than 1 min to prime and should be changed regularly to avoid it becoming blocked. We usually change our filters after 10 u of whole blood or after about 6 u of packed red cells. Both haemolysis and platelet depletion have been attributed to depth filters only, while there is evidence that the use of screen microaggregate blood filters may actually prevent post-transfusion thrombocytopenia [29]. Significant complement activation has been demonstrated only when heparinized blood was incubated with a nylon filter [55].

Although opinions vary widely concerning the indications for use of microfilters when giving stored blood, in adults we use them when 2 litre or more of blood is to be transfused, providing they can be used without delay and do not impede the rate of transfusion.

Increased affinity of haemoglobin for oxygen

Valtis and Kennedy [53] were the first to observe that the oxygen dissociation curve of stored blood was shifted to the left, reaching a maximum after storage for about 1 week in acid citrate glucose. This increased affinity of haemoglobin for oxygen is caused by depletion of 2,3-diphosphoglycerate (2,3-DPG) within the red cell and may last for several hours after transfusion [1]. The depletion of red cell 2,3-DPG during storage depends upon the preservatives used and the storage time. Modern anticoagulant preservative solutions, such as citrate phosphate glucose adenine, ensure adequate concentrations of 2,3-DPG for up to 14 days after collection of blood. The clinical significance of this increased affinity of stored red blood cells for oxygen is unclear, but it may result in temporary reduction in oxygen availability at a tissue level [51]. This may be detrimental in patients with severe cerebral disease, ischaemic heart disease, anaemia or hypoxia. The adverse effects of 2,3-DPG depletion are offset to some extent by the acidosis of stored blood. As both cold and alkalosis also shift the dissociation curve to the left, it would seem prudent to give these patients warmed blood that has been stored for no longer than 7 days, and to avoid the unnecessary use of bicarbonate.

Transfusion-transmitted diseases

All blood products except albumin and gammaglobulin can transmit infectious diseases. Viral infections are the most commonly transmitted, with the Hepatitis C virus (causing Non-A, Non-B Hepatitis) being the most serious in terms of frequency and morbidity. Transmission of HIV by transfusion has been extremely rare since the introduction of HIV antibody screening in 1985.

CASE REPORT

Although the adverse effects of a massive blood transfusion are well described in all of the major text books, in the authors' experience they are uncommon. We report a patient whose case illustrates the syndrome well (table V), although it should be emphasized that the patient concerned offered an extreme example of the difficulties.

The patient was an 8-month-old, female child presenting for liver transplantation because of end-stage liver disease resulting from biliary atresia. This had been treated previously at the age of 6 weeks by portoenterostomy (Kasai procedure). Unfortunately, this was unsuccessful and because of the infant's increasing disability and failure to thrive, orthotopic liver transplantation was considered necessary. The operation was technically difficult because of the previous surgery and the profound preoperative coagulation disturbances. The estimated blood volume in this child was 0.53 litre (a significant amount of ascites was present, artificially increasing the body weight).

From the start of the operation to the period when the vascular clamps were applied, approximately 10 blood volumes were lost. This was replaced with banked blood in excess of 72 h old because the patient had anti-E antibodies and fresh blood was not available. The ionized calcium decreased from 1.1 to 0.79 mmol litre^{-1}, despite the administration of calcium chloride 50 mmol. The plasma potassium concentration increased from 4.2 to 7.5 mmol litre^{-1}.

Because of concern that a further increase in potassium might occur when the liver was revascularized, prompt treatment was considered necessary, therefore 50% glucose 10 ml and insulin 2 u were administered. In addition, a large dose of frusemide (10 mg) was given. A further dose of glucose and insulin (50% of the previous dose) was administered 5 min before revascularization. The urinary potassium concentration did not increase (119 mmol litre^{-1} and 117 mmol litre^{-1} before and after the frusemide, respectively), but the volume of urine excreted increased considerably, thereby increasing the excretion of potassium. This, together with the administration of glucose and insulin, decreased the plasma potassium concentration to a value whereby revascularization proceeded uneventfully. In the event, there was a degree of overshoot necessitating the administration of potassium chloride during operation.

Despite efficient blood-warming and pyrexia before operation, the nasopharyngeal temperature decreased steadily and a further decrease was seen when the donor liver was revascularized (having been stored at 4 °C). After revascularization, the temperature did not decrease further.

Plasma sodium concentration increased throughout the procedure, from 130 mmol litre^{-1} at the beginning to 154 mmol litre^{-1} at the end; this reflects the sodium contained both in blood and blood products. Activated clotting time was maintained at an acceptable value throughout the procedure by infusion of fresh frozen plasma, cryoprecipitate and platelets. Base deficit increased until after the liver was revascularized, despite the administration of sodium bicarbonate 75 mmol. All blood was filtered through a 40-μm filter and acute lung injury did not develop in this patient, despite the transfusion of almost 10 circulating blood volumes.

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SHORT COMMUNICATIONS

RETROGRADE INTUBATION—A FACILITATED APPROACH

S. S. DHARA

SUMMARY

The procedure of retrograde tracheal intubation has been facilitated by the use of a multilumen catheter guide. When used as an anterograde guide, it would easily follow the retrograde guide and would direct placement of the tracheal tube atraumatically. A new technique is described that allows stabilization of the anterograde catheter and its insertion deep inside the trachea to prevent dislodgement of the tracheal tube from the laryngeal inlet. This catheter guide may also be used as a conduit for high-frequency jet ventilation with monitoring of the airway pressure, thus providing wider margins of safety in patients with difficult upper airways. (Br. J. Anaesth. 1992; **69**: 631–633)

KEY WORDS

Intubation: retrograde, translaryngeal guided.

In a situation of difficult tracheal intubation, a retrograde intubation technique, also known as translaryngeal guided intubation, is an accepted mode of establishing an airway [1]. There are two parts to the procedure: "guidance" consists of retrograde insertion of a catheter from the larynx to the mouth or nose, and the "blind" part is the insertion of a tracheal tube without visualization of glottis. There are, however, some difficulties with this technique, including: the ability to pass a catheter retrogradely out through the mouth or nose; availability of an atraumatic anterograde catheter to follow the retrograde guide easily; prevention of dislodgement of the anterograde catheter or the tracheal tube after release of the retrograde guide at the cricothyroid membrane; and the ability to deliver oxygen or to ventilate the lungs during this procedure. In an attempt to deal with these problems, we describe a streamlined technique of retrograde intubation with the help of a multilumen catheter guide system. This technique has been used successfully in 40 patients over the past few years.

METHODS AND RESULTS

The multilumen catheter guide and the adaptor (fig. 1)

A multilumen catheter guide which is flexible enough to follow easily a retrograde guide and yet firm enough to serve as an introducer for a tracheal tube has been designed.

The catheter is radio-opaque, 35 cm in length, tapered at both ends and is graduated at 10, 20, 25 and 30 cm from the lower end. The maximum external diameter is 4.75 mm. There are three longitudinal channels—a large central one which remains after the extrusion of two small circular channels, each with a diameter of 1.2 mm. The central channel runs throughout the length of the catheter whereas the smaller channels, at the upper end, start from the side at slightly different levels and terminate on each side of the catheter, one 1.5 cm and the other 3 cm from the tip. At the upper end, the entrance to the side channel terminating closest to the tip is marked for easy identification. Near the termination, the central channel has two small openings on two sides.

It is possible to isolate the three channels by use of a lightweight plastic adaptor which has snugly fitting rubber "O" rings providing small airtight compartments leading to the respective channels. All three ports on the adaptor have Luer lock fittings.

The length of a catheter guide is important, as it is easier to manoeuvre a shorter catheter, but a longer length is necessary for use as a stylet to guide a tracheal tube. Hence, a provision to extend or shorten the length of the catheter during the procedure would be desirable. The length of the catheter guide can be increased by connecting a 14-French gauge polyvinyl chloride (PVC) tubing (e.g. a suction catheter) into the tapered proximal end. The union does not separate easily, but may be separated, when needed, with little effort.

The procedure

The preparation of the patient consists of light premedication, an i.v. infusion, monitoring by electrocardiogram, pulse oximetry and non-invasive arterial pressure monitor and analgesia to the nostril, the mouth and the upper airway. The skin in front of the cricothyroid membrane is infiltrated with 1% lignocaine 1–2 ml. The larynx is stabilized between the thumb and index finger of one hand and the cricothyroid membrane is punctured with a 16-gauge, 5-cm i.v. cannula (Vasocan, B Braun Melsungen) held at 45° angle with the tip pointing cephalad.

Recently, puncture through the cricotracheal membrane has been recommended because of re-

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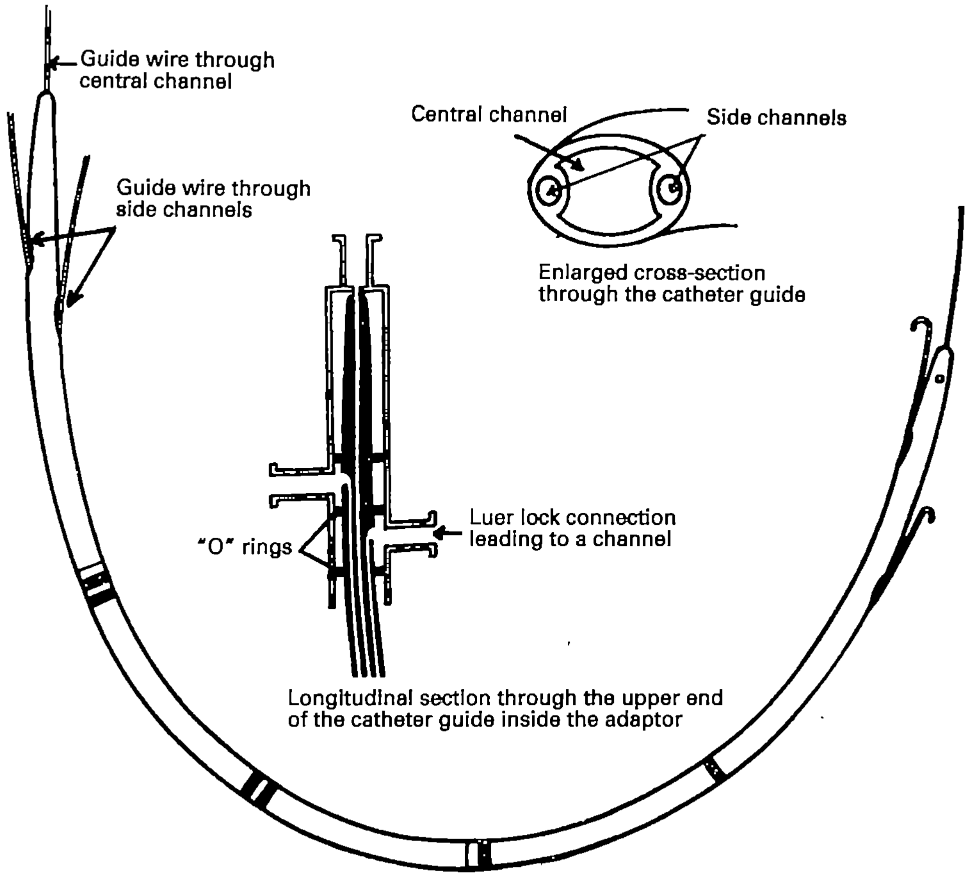
Guide wire through central channel
Guide wire through side channels
Central channel
Side channels
Enlarged cross-section through the catheter guide
"O" rings
Luer lock connection leading to a channel
Longitudinal section through the upper end of the catheter guide inside the adaptor

FIG. 1. Schematic diagram of the multilumen catheter guide and the adaptor.

duced vascularity of the tissue at the site of puncture and better depth of insertion of the tracheal tube inside the larynx [2]. The cannula is pushed further at an obtuse angle closer to the axis of the larynx. When the plastic cannula is placed just above the vocal cords, the retrograde guide tends to come out via the mouth. If the plastic cannula is pushed up to the hilt, it rests on the posterior pharyngeal wall and the guide wire tends to come out through the nostril.

The needle stylet is withdrawn. After the position of the catheter has been confirmed by aspiration of air, a J-tipped vascular guide-wire, 70 cm in length and 0.8 mm in diameter (B Braun Melsungen), is passed through the lumen of the catheter and advanced until it emerges from the nose or mouth. Retrieving the retrograde guide by tying it to a plastic cannula passed nasally [1] may be traumatic to the nasal mucous membrane and turbinates; this can be avoided if the thin retrograde guide is fed into the lumen of the plastic catheter until the retrograde guide protrudes from the nasal end of the suction catheter, which is then withdrawn completely, leaving the retrograde guide protruding from the nose [3]. To be able to place the retrograde wire directly through the nose is very useful in a patient who is unable to open the mouth wide enough for retrieval of the catheter passed through the nose. The lower end of this retrograde guide must be secured outside the skin with a pair of forceps.

A multilumen catheter guide is prepared in advance with a second guide-wire similar to the first, partially inserted into the side channel opening closest to the tip. The prepared catheter guide is lubricated with water-soluble jelly, threaded over the retrograde wire through its central channel and pushed gently over the guide until it reaches just behind the puncture site on the cricothyroid membrane. This is detected easily by the i.v. cannula being pushed out by the advancing tip of the catheter guide. If any resistance is felt during the negotiation forward, a rotating movement of the catheter guide over the retrograde wire with a simultaneous gentle push helps it to advance. The catheter guide is rotated to position the side channel loaded with the guide wire posterior to other channels. This manoeuvre aligns the tip of the second guide wire with the laryngeal inlet and thus, when advanced, the tip should be inside the larynx and the trachea.

As the tip of the guide-wire reaches the lower trachea or touches the carina, a cough, subdued by application of local anaesthetics, is produced, confirming its location. The retrograde guide-wire is now withdrawn from the top end as the catheter guide is "railroaded" over the second guide-wire into the trachea. The second guide-wire may now be withdrawn.

At this stage, the adaptor may be slipped over the catheter guide and oxygen may be delivered by jet ventilation through the central channel, if needed. One of the side channels may be connected to the airway pressure monitor and the other to the capnograph. The high-frequency jet ventilation may be delivered either from an automatic jet ventilator or a manual jet insufflator. However, monitoring of airway pressure is essential to prevent barotrauma.

For guiding a tracheal tube, the adaptor is removed and the length of the catheter guide is extended by connecting a 14-French gauge plastic suction catheter without the flanged end to the tapered upper end of the catheter guide. A well lubricated armoured tube or a softened PVC tracheal tube may now be passed easily over the guide into the trachea. Negotiating the tracheal tube through the nostril or the largyngeal inlet may be distressing to some patients despite sedation and topical local anaesthetic. A sleep dose of an i.v. induction agent, for example thiopentone or propofol, may be required before the tracheal tube is inserted just into the trachea, for the comfort of the patient.

COMMENT

A facilitated approach to retrograde intubation has been described using a specially designed catheter guide. This technique has been used mostly as a procedure of choice, but sometimes in rather poorly controlled situations when other methods of intubation had failed. The multiple channels in the catheter may be used for jet ventilation, measurement of airway pressure, sampling of gas, instillation of further doses of local anaesthetic or tracheal suction during or at the end of the procedure.

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CONTINUOUS SUBARACHNOID INFUSION OF 0.125% BUPIVACAINE FOR ANALGESIA DURING LABOUR

S. McHALE, V. MITCHELL, S. HOWSAM AND F. CARLI

SUMMARY

We have studied 20 primiparous women requesting pain relief for labour, to determine the feasibility of subarachnoid infusions of bupivacaine for analgesia. A 28-gauge catheter was inserted into the subarachnoid space through a modified 22-gauge Sprotte needle. After a bolus dose of up to 1.5 ml of 0.25% bupivacaine, a continuous infusion of 0.125% bupivacaine was commenced. If analgesia became inadequate, additional 0.5-ml boluses of 0.25% bupivacaine were given (mean number of top-ups 2.8; range 0–6). Persistent perineal pain occurred in four women and this was relieved by 0.5% hyperbaric bupivacaine. Analgesia was good or excellent in 15 of 20 mothers within 10 min and in 19 of 20 within 30 min, and it remained good or excellent throughout labour and delivery. Motor block was complete in three of the women who needed hyperbaric 0.5% bupivacaine. There were no difficulties with insertion of the catheter, no episodes of significant hypotension (systolic arterial pressure less than 100 mm Hg) or postdural puncture headache. Seven mothers delivered their babies vaginally, eight required assistance with forceps and five needed a Caesarean section. (Br. J. Anaesth. 1992; **69**: 634–636)

KEY WORDS

Anaesthetic techniques: subarachnoid. Anaesthetics, local: bupivacaine. Analgesia: obstetric. Equipment: catheters.

Subarachnoid infusions of local anaesthetic solution may have some advantages over extradural analgesia for labour, namely speed of onset, reliability and lack of maternal and fetal toxicity because of the small amounts of drug required. Until recently, the design and size of the spinal needles resulted in an unacceptably high incidence of postdural puncture headaches (PDPH) in labouring women, and therefore continuous spinal infusions have not been popular as a technique for analgesia. Some workers have investigated the use of 32-gauge catheters for intermittent administration of 0.25% bupivacaine [1, 2], 1% lignocaine [3] and diamorphine [4] and found the technique to be feasible. This study was undertaken to assess the feasibility of a continuous intrathecal infusion of bupivacaine for analgesia during labour in a group of primiparae.

METHODS AND RESULTS

This study was approved by the local Ethics Committee and informed consent was obtained from all women. We studied 20 primiparae at more than 36 weeks gestation, in labour with a cervical dilatation less than 5 cm and with a single, normally formed baby who presented cephalically.

After an i.v. preload of at least 500 ml of compound sodium lactate solution, each woman was placed in the left lateral position, and a standard aseptic technique was used to introduce a modified 22-gauge Sprotte needle through the midline into the subarachnoid space at the L2–3 or L3–4 interspace. After free flow of cerebrospinal fluid (CSF) was obtained, a 28-gauge spinal catheter (Kendall) was inserted through the needle. The needles were modified to ensure that, as the catheter was passed along the barrel, it would be directed out through the side hole. The needle and the Teflon coated stylet were then removed and the catheter was withdrawn so that the 10-cm mark was visible at the site of skin puncture. To confirm placement of the catheter in the subarachnoid space, CSF was aspirated and a 0.2-μm filter was attached.

All women were placed in the semi-recumbent position, supported by a wedge at an angle of 30°, and 0.25% bupivacaine 1.0 ml was injected. Maternal analgesia was assessed at 5 and 10 min and if, after 10 min, analgesia was unsatisfactory, an additional 0.25% bupivacaine 0.5 ml was given. When analgesia was satisfactory, an infusion of 0.125% bupivacaine was started at a rate of 1.5 ml h^{-1} and continued until delivery. If the analgesia became inadequate during labour, a top-up of 0.25% plain bupivacaine 0.5 ml was given. Persistent perineal pain was relieved with 0.5% hyperbaric bupivacaine 0.1–0.5 ml. The mother was allowed to adopt any position she found comfortable. Systolic arterial pressure was checked every 2 min for the first 10 min, every 5 min for the next 20 min and every 30 min during the period of the infusion. The following were assessed at 5, 10 and 30 min after the initial dose and thereafter every 1 h: level of sensory

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loss to cold on each side using an ethyl chloride spray; extent of motor block using a Bromage score (0 = absence of motor block; 1 = partial motor block; 2 = almost complete motor block; 3 = complete motor block); presence of proprioception in the great toe; patient's satisfaction on a four-point scale (excellent, good, fair or poor). When an instrumental or an operative delivery became necessary, the infusion was discontinued and up to 2.0 ml of 0.5 % hyperbaric bupivacaine was used to extend the block. The fetal heart rate was monitored continuously using a scalp electrode. In this unit it is the practice to manage labour actively, whereby primiparous women are examined 2-hourly, and if the cervix fails to dilate by at least 1 cm each hour, an infusion of oxytocin is commenced [5].

After delivery, the time to full return of motor function was recorded, and the mothers were followed up until discharge home to assess for any neurological deficit or headache.

Mean maternal age was 25.1 yr (range 17–32 yr), mean body weight 64.8 kg (range 46–82 kg) and mean height 158.2 cm (range 148–166 cm). Fourteen mothers started labour spontaneously and the others had labour induced. Of those women with a spontaneous onset of labour, 14 had labour augmented with oxytocin.

Eleven mothers described analgesia as excellent or good 5 min after the initial 1.0 ml of 0.25 % bupivacaine. Four others described it as excellent or good 10 min after the initial dose, and another four at 30 min after an additional 0.25 % bupivacaine 0.5 ml. The block was always bilateral and the upper level of sensory loss to ethyl chloride spray was T3–9. Four women complained of persistent perineal pain which was relieved only by boluses of 0.5 % hyperbaric bupivacaine 0.1–0.5 ml. One mother complained of suprapubic pain which was not relieved by 0.5 ml of either 0.25 % plain bupivacaine or 0.5 % hyperbaric bupivacaine, despite an upper level of sensory loss of T6. It was decided to insert an extradural catheter at a higher space, and 2 % lignocaine 3 ml relieved the pain. The spinal infusion was then maintained effectively throughout the rest of her labour.

The mean duration of the bupivacaine infusion was 3 h 13 min (range 1 h 3 min–7 h 14 min) and mean number of top-ups was 2.8 (range 0–6). The shortest time before a top-up was required (when adequate analgesia had been achieved) was 30 min. The maximum dose given was bupivacaine 27.25 mg and the minimum, bupivacaine 7.5 mg. Proprioception was lost on at least one side in six of the mothers, whilst three had a Bromage score of 3, five of 2, six of 1 and six of 0 during labour. The systolic arterial pressure remained greater than 100 mm Hg in all the women, despite an upper sensory level of T3 in four.

There were seven spontaneous deliveries and eight forceps deliveries, three of which were rotational. The indication for all of the forceps deliveries was fetal distress. Five women needed a Caesarean section: one was for obstructed labour and the others for fetal distress. In four, the intrathecal block was extended with 0.5 % hyperbaric bupivacaine 1.0–2.0 ml, which produced an upper level of sensory loss to at least T4 in less than 13 min. The highest level of sensory loss was T3. The fifth mother wanted a general anaesthetic, which was administered without difficulty. All babies had Apgar scores of at least 8 at 5 min after delivery and none needed to go to the special care unit. All the catheters were removed intact and full motor power had returned within 2–3 h following delivery.

All mothers considered analgesia as excellent or good when questioned the following day. There were no neurological sequelae and no PDPH.

COMMENT

We have found that continuous subarachnoid infusion of bupivacaine was a feasible method for provision of analgesia during labour.

The modified 22-gauge Sprotte needle was easy to insert and the 28-gauge catheters were threaded without difficulty through the side hole. CSF was aspirated easily down the catheters, confirming correct placement, and this may account for the number of successful blocks. This is in contrast with other studies of 32-gauge spinal catheters with a technical failure rate of 25 % [3], and difficulty in threading the catheters beyond the tip of the spinal needle in five of 14 subjects [2].

We have no explanation for the suprapubic pain experienced by one woman which, despite an upper sensory level of block at T6 on both sides, was relieved only by 2 % lignocaine 3 ml injected extradurally. There was no change in the height of the block and the subarachnoid infusion was continued effectively during the rest of her labour. There was no evidence to suggest a dural puncture at the time of the extradural insertion, and the woman did not subsequently develop any type of headache.

Four mothers complained of persistent perineal pain as their labour progressed, which was not treated adequately with 0.25 % plain bupivacaine but required 0.5 % hyperbaric bupivacaine to produce analgesia. This resulted in complete motor block in three of the women and an almost complete block in the other. Of the 16 women not requiring hyperbaric bupivacaine, only four had a Bromage score of 2. Huckaby and colleagues also used hyperbaric 0.5 % or 5 % lignocaine to relieve the perineal pain that occurred in 10 of 20 parturients who received intermittent intrathecal 1 % lignocaine during labour [3]. It seems, therefore, that neither plain lignocaine nor plain bupivacaine is adequate when used as the sole agent intrathecally.

Intermittent intrathecal diamorphine has been given to 20 women during labour and analgesia was reported as excellent or good in 16 of them within 30 min [4]. However, despite further top-ups of diamorphine, 80 % of the mothers needed additional 0.5 % plain bupivacaine to maintain analgesia in the first stage and opioid side effects were common: 15 mothers had pruritus, 15 had nausea and vomiting and eight had mild sedation.

In the present study, there were no PDPH, despite the use of a 22-gauge Sprotte needle. Our results confirm previous work indicating that the type of the needle might be relevant in the incidence of PDPH in the pregnant population [6].

The low spontaneous vaginal delivery rate (35 %) observed in this study was unexpected. This may be a reflection of the effectiveness of the analgesia in the second stage, with the infusions being maintained throughout. Other workers have reported a spontaneous delivery rate of 100 % with intermittent lignocaine [3], but they did not confine themselves to primiparous women as in this study. Fetal distress was diagnosed by the obstetricians in 60 % of subjects, and was not associated with maternal hypotension or aorto–caval compression. Caesarean section was considered necessary if there was both a poor cardiotocograph tracing and a fetal scalp pH reading of less than 7.25 during the first stage of labour. Forceps deliveries were indicated if there were persistent decelerations in fetal heart rate after uterine contractions in the second stage of labour with or without an abnormal fetal scalp pH reading. The forceps rate of 40 % is probably not atypical and the Caesarean section rate of 25 % could have occurred by chance.

In conclusion, this study shows that intrathecal infusion of a dilute solution of bupivacaine appears to be an effective method of maintaining analgesia during labour, and the height of the block can be extended rapidly in the event of an instrumental or an operative delivery. The likelihood of catheter breakage which has been reported with 32-gauge catheters, should be reduced when 28-gauge catheters are used. Larger studies are required to confirm this and any increased risk of infection associated with intrathecal infusions. It remains to be seen if the addition of opioids or selection of other local anaesthetics might provide better analgesia during labour and maintain a greater rate of spontaneous vaginal delivery.

ACKNOWLEDGEMENT

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EFFECT OF INTERPLEURAL MORPHINE ON POSTOPERATIVE PAIN AND PULMONARY FUNCTION AFTER THORACOTOMY

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SUMMARY

We have investigated the effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy. At the end of surgery, an interpleural catheter was inserted in 17 patients and, in a double-blind and randomized manner, either a bolus of morphine 2.5 mg interpleurally (i.p.) and normal saline i.v. (group I) or, as a control for systemic absorption, morphine 2.5 mg i.v. and i.p. saline (group II) was injected. After the initial bolus, a continuous infusion of morphine 0.5 mg h^{-1} i.p. and saline i.v. (group I) or morphine 0.5 mg i.v. and saline i.p. (group II) was maintained for 24 h. Postoperative pain was assessed by a visual analogue scale, a numerical rating scale and the McGill Pain Questionnaire. Pulmonary function was assessed by spirometry. Supplementary analgesics, side effects, degree of sedation, vital signs and chest tube drainage were recorded. All variables were assessed on the day before surgery and 1, 2, 3, 4, 5, 6 and 24 h and 7 days after surgery. Supplementary morphine was given upon request. There was no significant difference in any pain measure or postoperative pulmonary function variable between the groups. We conclude that, after thoracotomy, interpleural morphine does not provide superior analgesia or improve pulmonary function compared with systemic morphine. (Br. J. Anaesth. 1992; **69**: 637–639)

KEY WORDS

Analgesics: morphine. Anaesthetic techniques: interpleural analgesia. Pain: postoperative.

Recently, we and others have demonstrated that opioid agonists may produce peripheral antinociceptive effects in inflamed tissue of rats [1]. These effects are mediated by opioid receptors located on peripheral terminals of primary afferent neurones [2]. In patients undergoing arthroscopic knee surgery, we showed that intra-articularly applied morphine 0.5–1 mg produced more profound postoperative analgesia than the same dose given i.v. [3].

In this study we hypothesized that, after thoracotomy, interpleurally (i.p.) injected morphine might occupy receptors on intercostal nerves and produce analgesia. We investigated the effect of morphine i.p. on postoperative pain and pulmonary function. To exclude the possibility that the effect of i.p. morphine was mediated by central opioid receptors, the same dose of morphine was given i.v. in a control group.

METHODS AND RESULTS

The study was approved by our Institutional Ethics Committee and written informed consent was obtained from each patient. We studied 20 patients undergoing anterolateral thoracotomy, allocated randomly to two groups. After premedication with flunitrazepam 1 mg, anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1.5–3 $\mu g\ kg^{-1}$, followed by suxamethonium 1 mg kg^{-1}. Anaesthesia was maintained with 0.6–1.2 vol % isoflurane, fentanyl (maximal total dose 10 $\mu g\ kg^{-1}$) and pancuronium. Incisions were made in the 5th anterolateral intercostal space. Chest tubes were positioned posteriorly and anteriorly in the pleural space.

Before closure of the thoracotomy, an interpleural catheter (18-gauge extradural catheter, Braun-Melsungen, Melsungen, Germany) was inserted percutaneously via a Tuohy needle in the anterior axillary line. The catheter tip was positioned cranial to the incision in the anterior midclavicular line.

Before tracheal extubation, the following solutions were injected simultaneously i.p. and i.v.: group I received morphine hydrochloride 2.5 mg in normal saline 40 ml i.p. and normal saline i.v.; group II received normal saline 40 ml i.p. and morphine hydrochloride 2.5 mg i.v. The choice of doses of morphine was based on previous studies [1, 3]. After their injection, chest tubes were clamped for 20 min. After arrival of the patient in the recovery room simultaneous i.v. and i.p. infusions were started and maintained for 24 h: group I received morphine hydrochloride 0.5 mg in normal saline 20 ml per hour i.p. and normal saline i.v.; group II received normal saline 20 ml h^{-1} i.p. and morphine hydro-

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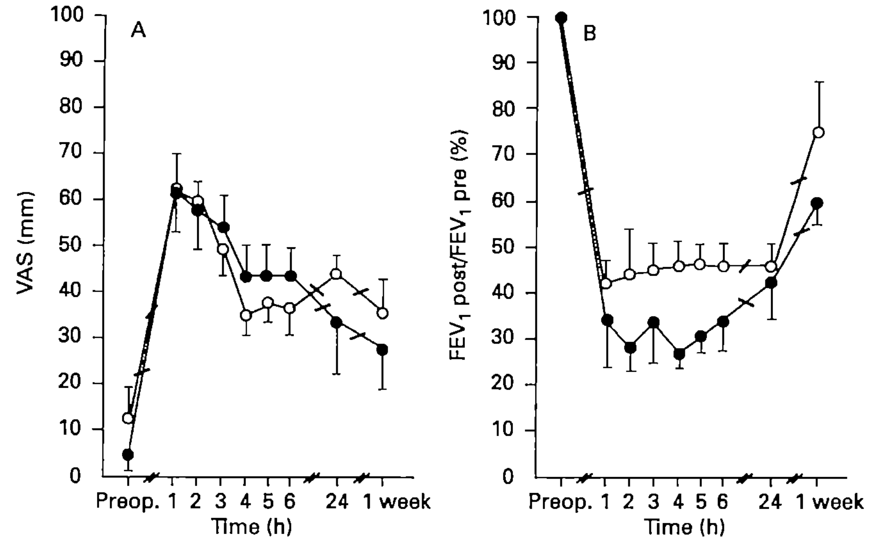

FIG. 1 A: Pain scores as determined by visual analogue scale (VAS). B: Forced expiratory volume during the first 1 s (FEV$_1$)—postoperative value (post) as a percentage of preoperative value (pre). ○ = I.v. morphine; ● = interpleural morphine. Mean values and SEM.

chloride 0.5 mg h^{-1} i.v. The codes were broken at the end of the observation period (7 days). The patients were positioned supine with the head 30° elevated. A suction of 15–20 cm H_2O was applied to the chest tubes. During the first 24 h, the patients received supplementary morphine hydrochloride in increments of 2.5 mg i.v. upon request.

Postoperative pain was assessed using a visual analogue scale ranging from no pain (0 cm) to unbearable pain (10 cm), a numerical rating scale (0–100), and a German adaptation of the McGill Pain Questionnaire [4]. All scores were taken by the same blinded investigator on the day before surgery and at 1, 2, 3, 4, 5, 6, 22–24 h and 7 days after surgery. Pulmonary function was assessed at these intervals using a bedside spirometer (Microspiro H I-298, Chest Corp., Tokyo, Japan) and arterial blood-gas analysis. Somnolence was assessed using a five-point scale from awake and oriented to not arousable. Side effects were monitored, including respiratory depression, nausea, pruritus, rash and urinary retention.

To score the McGill Pain Questionnaire, the pain rating indices were calculated according to Melzack [4]. The total consumption of supplementary morphine during the first 24 h after surgery was recorded. Comparisons between groups were made using the Mann–Whitney *U* test. $P < 0.05$ (two-tailed) was considered significant. Data are given as mean (SEM).

Three patients in group I were excluded because of surgical revision or respiratory failure. Patient characteristics, vital signs, sedation score (grade I–II), and preoperative pain scores and pulmonary function did not differ significantly between groups. Surgical procedures included wedge resections (n = 7), lobectomies (n = 8) and the combination of both (n = 2). The duration of surgery was 132 (SEM 17) min in group I and 84 (11) min in group II (*U* test, ns). There were more lobectomies in group II (six of 10 patients) than in group I (two of seven patients). The total intraoperative dose of fentanyl did not differ between groups (group I, 590 (110) μg; group II, 580 (50) μg). There were no major side effects.

After operation, there was no difference between groups in any pain score at any time (fig. 1). Supplementary analgesic requirements did not differ between groups (*U* test, data not shown). Pulmonary function variables (fig. 1) and blood-gas values did not differ significantly between groups. Total chest tube drainage after 24 h was 680 (138) ml in group I and 775 (120) ml in group II (ns).

COMMENT

We have found no difference in postoperative pain scores, pulmonary function or supplementary analgesic requirements in patients given morphine i.p. or i.v. after thoracotomy. These results indicate that i.p. administered morphine in the doses used did not provide analgesia superior to that obtained with i.v. morphine. This finding is at variance with our results in patients after arthroscopic knee surgery, in which intra-articular morphine yielded analgesic effects superior to the same dose given i.v. [3].

A probable mechanism of action of opioids in the periphery is activation of opioid receptors on terminals of primary afferent neurones [2]. We hypothesized that morphine might occupy such receptors on intercostal nerves. Even though we have used a 2.5-fold greater concentration of morphine compared with our previous study [3], postoperative bleeding and secretion may lead to a dilution of the morphine solution and may thus reduce the concentration of morphine at the receptors.

Unlike local anaesthesia, which interrupt action potential generation and propagation at both the axon and nerve terminal [5], opioids appear to exert their inhibitory effects predominantly at the nerve terminals [1]. Gravity-dependent pooling in dependent areas of the pleural space may preclude an action of morphine upon nerve terminals.

In contrast with the knee joint after arthroscopic surgery, the interpleural cavity is not a closed space after thoracotomy. Any drug injected into the interpleural space may be lost partially through the chest drains. Thirty to forty percent of the total dose of bupivacaine injected into the pleural space may be recovered in the thoracostomy fluid [6]. Even though we did not measure morphine concentrations in the thoracostomy fluid, one may speculate that a similar amount of morphine was lost through the chest tubes.

In conclusion, we found that low doses of interpleural morphine after thoracotomy did not improve analgesia or pulmonary function compared to the same dose given i.v..

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AN ACTIVE HEAT AND MOISTURE EXCHANGER

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SUMMARY

We have carried out a laboratory evaluation of an active heat and moisture exchanging filter (aHMEF). The device consists of a conventional heat and moisture exchanging filter (HMEF) with an additional heating element and water supply. It was compared with a standard HMEF using a model lung. The aHMEF with the heating element alone, reduced 2-hourly water loss compared with the HMEF ($P < 0.001$*); with both the heating element and additional water, this was reduced further (*$P < 0.001$*). The mean catheter mount temperature with the HMEF and heater was 32.7 (SD 1.8) °C and with the complete aHMEF was 34.6 (1.6) °C. The maximum temperature with the heating element in use was 37.7 °C. We conclude that the aHMEF provided effective, controllable and convenient humidification of inspired gases.* (Br. J. Anaesth. 1992: **69**; 640–642)

KEY WORDS
Equipment: humidifiers.

Patients receiving mechanical ventilation with dry gases need additional humidification to reduce heat and water loss and the resulting adverse changes in pulmonary function [1]. Different types of humidifier are associated with specific advantages and disadvantages [1]. We have evaluated a new humidification device, an active heat and moisture exchanging filter (aHMEF), that combines the efficiency of a hot water humidifier with the simplicity of an HMEF.

Description

The prototype aHMEF is based on a standard HMEF (Humid-Vent Filter, Guibeck Respiration AB, Upplands Vasby). The casing was modified to accommodate a water drip inlet and an aluminium scabbard, covered in stretched woven cotton, into which a self-regulating low voltage heater probe is inserted. The heater probe consists of two parallel electrodes separated by current conducting carbon particles mixed in a polymer (Raychem Ltd, Swindon, U.K.). The resistance of the probe, and so its heat output, changes with temperature. Because the mechanism depends on a physicochemical property, the temperature is regulated reliably at 70 ± 1 °C. The heater element is powered by a 12-V supply and has a current drain of 1 A, thus posing no electrical hazard to the patient.

Sterile water is delivered by a mains powered roller pump to the heated scabbard, where it is evaporated. The pump (Becton-Dickinson, Grenoble, France) delivers sterile water at 1–7 ml h^{-1}. The quantity of water delivered can be varied and is adjusted according to the patient's minute volume according to the formula: $(\dot{V}-1)/2$.

METHODS AND RESULTS

The aHMEF was compared with a standard HMEF using a simulated lung connected in series. This consisted of a 2-litre bag with a heated water humidifier (Fisher Paykel, Auckland, New Zealand) maintained at 37 °C. These were contained within a thermally insulated box that was also maintained at 37 °C. The box and its contents were placed on a scale, sensitive to 0.1 g, to measure water loss from the test lung. The lung was ventilated with a Cambridge ventilator at rates of 10 and 17 b.p.m. and with tidal volumes of 0.5, 0.75 and 1 litre. A disposable breathing circuit (Intersurgical, Twickenham, U.K.) connected the ventilator to the test lung. Weight loss of the test lung was measured at 0.5, 1, 1.5 and 2 h for each tidal volume and frequency. Each test was repeated five times and the mean water loss was calculated.

The lung was ventilated without a humidifier, with an HMEF (Gibeck, Stockholm, Sweden), with the aHMEF using the heater alone and with the aHMEF with the heater and added water. To test thermal safety, the aHMEF was placed in the breathing circuit and left switched on, without ventilation, for 1 h. Ventilation was then started and the temperature at the catheter mount was measured for the first five breaths. The mean and maximum temperatures in the same position were recorded also for each 30-min period. Statistical analysis was performed using one-way analysis of variance and Student's t test for unpaired data.

The water loss from the simulated lung under the various test conditions is shown in figure 1. Water loss tended to increase with increased minute

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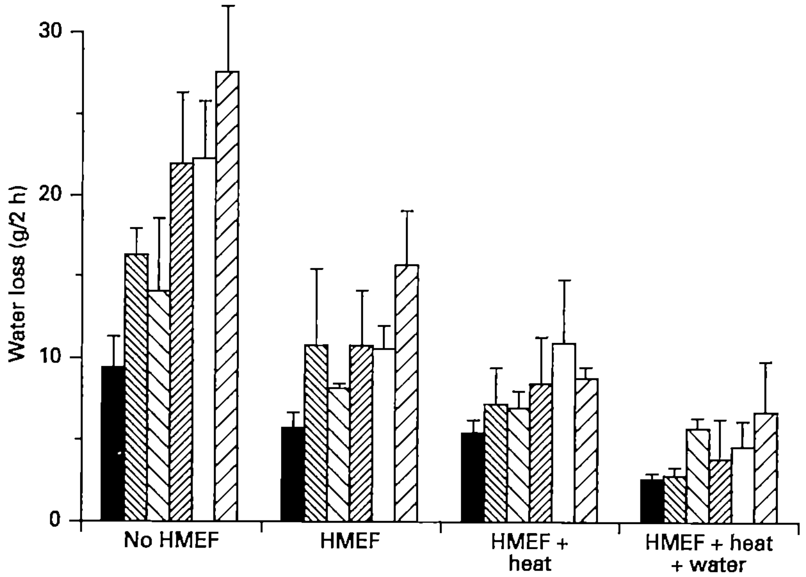

FIG. 1. Two-hourly water loss from the test lung using combinations of tidal volumes of 0.5, 0.75 and 1.0 litre and ventilatory frequencies of 10 and 17 b.p.m. (minute volumes: ■ = 5 litre min^{-1}; ■ = 7.5 litre min^{-1}; ▧ = 8.5 litre min^{-1}; ■ = 10 litre min^{-1}; □ = 12.5 litre min^{-1}; ▨ = 17 litre min^{-1}). Analysis of variance demonstrates a difference ($P < 0.001$) between each group.

volume. The standard HMEF decreased water loss compared with control values. The addition of the heater to the HMEF produced a further decrease and another decrease in water loss was produced when the aHMEF was used with water and heat.

The mean catheter mount temperature without an HMEF was 28.4 (SD 1.6) °C. The mean temperature increased with an HMEF (30.7 (2.1) °C) ($P < 0.001$); with the HMEF and heater (32.7 (1.8) °C) ($P < 0.001$) and with the complete aHMEF (34.6 (1.6) °C) ($P < 0.001$). The maximum temperature recorded with the HMEF and heater was 36.1 °C; that with the complete aHMEF was 37.7 °C. During the pre-heating test, the maximum recorded temperature was 34.6 °C.

COMMENT

The ideal humidifier should be efficient at retaining heat and moisture, represent no physical, electrical, mechanical or microbiological hazard to the patient, and be easy to use and economical. Hot water humidifiers are efficient, but pose a potential microbiological and thermal hazard [2, 3], may have a high internal compliance [4] and are costly and inconvenient. By comparison, HMEF are safe, cheap and convenient [5], but they may not provide adequate humidification for all patients. The aHMEF described has the advantages of an HMEF, but is considerably more effective and allows control of the delivered absolute humidity.

In this study, heat and moisture loss from the test lung were reduced by an HMEF, further reduced by the addition of a heater and reduced again by adding water to the heater. The efficiency of HME is well documented [5]. The addition of a heater to the device may have increased the efficiency of heat and moisture exchange by increasing the temperature gradient across the device and by evaporating liquid water formed within the device. The further addition of exogenous water significantly improved efficiency.

The aHMEF is intrinsically safe. The heating element is regulated by a physicochemical property, maintaining temperature in the range 69–71 °C without complex equipment and the associated risk of malfunction. In this study, airway temperatures did not exceed 37.7 °C. Microbiological safety is ensured by a filter to protect both the patient and the ventilator from contamination. The risk of colonization of the ventilator tubing is minimized as there is no condensate on the ventilator side of the humidifier. In addition, as the catheter mount contains heated water vapour, condensation at this site is minimized. Electrical safety is maximized by the use of a 12-V source for the heater. This also allows the device to be battery powered for transport of patients.

The aHMEF system appeared to provide controllable and efficient humidification in a safe and economical way for patients undergoing artificial ventilation with dry gases. It may be used to replace an HMEF or a hot water humidifier. Because the aHMEF delivers efficient, controllable humidification, it may be useful particularly for patients with variable requirements, such as the critically ill and those who may receive inadequately humidified inspired gases at present, such as paediatric patients and patients with pulmonary pathology undergoing prolonged surgical procedures.

This device is protected by patents Nos 09000619 and 09001198, Belgian Office.

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HEPATIC FUNCTION AND INDOCYANINE GREEN CLEARANCE DURING AND AFTER PROLONGED ANAESTHESIA WITH PROPOFOL

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SUMMARY

We have studied the effects of propofol on hepatic function and clearance of indocyanine green (ICG) in 13 consecutive patients undergoing prolonged plastic and reconstructive surgery. Hepatic function was assessed using serum concentrations of liver-specific glutathione-S-transferase (GST). There were no significant changes in GST activity or plasma clearance of ICG throughout the study. (Br. J. Anaesth. 1992; **69**: 643–644)

KEY WORDS

Anaesthetics, intravenous: propofol. Liver: function. Surgery: prolonged.

Renewed interest in the use of i.v. techniques to provide balanced anaesthesia has been prompted partly by concern on the potential of volatile anaesthetics to cause tissue and organ toxicity. Fulminant hepatotoxicity, although well documented, is rare. Recent reports have suggested that brief or prolonged exposure to halothane causes increases in liver-specific glutathione-S-transferase activity, which suggest a more subtle type of halothane-induced liver injury [1, 2].

The rate of removal of ICG from plasma may be used to estimate hepatic blood flow, as it is removed almost exclusively by the liver and its volume of distribution is close to that of plasma volume. The bolus method, although subject to errors, is adequate to detect changes in individuals. Clearance after peripheral bolus injection has been validated against hepatic vein catheterization in animals and normal subjects.

Having established that halothane and isoflurane may have particular disadvantages when administered over a prolonged period [2, 3], we designed this study to evaluate the effects of a continuous infusion of propofol on hepatic function and ICG clearance during and after prolonged anaesthesia.

METHODS AND RESULTS

We studied 13 adult patients, mean age 60.1 yr (range 40–70 yr) and weight 75.8 (SD 9.39) kg, undergoing prolonged head and neck reconstructive surgery (approximately 10 h duration). University Medical Ethics Committee approval and informed consent were obtained. Patients with evidence of liver disease, recent alcohol abuse, known hyperlipidaemia, or who had received an inhalation anaesthetic within the previous 3 months were excluded. No patient was taking drugs known to induce liver enzymes.

Premedication consisted of temazepam 20 mg, 1 h before induction of anaesthesia. All patients received a similar anaesthetic comprising an initial bolus of alfentanil 30 μg kg^{-1} followed by an alfentanil infusion at 30–50 μg kg^{-1} h^{-1}. Anaesthesia was induced with propofol 2.0 mg kg^{-1} and maintained with a continuous infusion at an initial rate of 10 mg kg^{-1} h^{-1} for 10 min, followed by 8 and 6 mg kg^{-1} h^{-1} at 10-min intervals. Thereafter, the rate of propofol was adjusted to the clinical haemodynamic response. Atracurium 0.5 mg kg^{-1}, followed by increments if required, was used to facilitate nasotracheal intubation and provide neuromuscular block. Normocapnic ventilation was maintained with oxygen enriched air ($F_{I_{O_2}}$ 0.4). Arterial blood-gas tensions and pH were measured at 5-h intervals during surgery and daily thereafter.

During and after operation, the volume of fluid administered, including blood, was titrated against haemodynamic variables and urinary output. PCV was maintained at 30–33 %.

Heart rate and rhythm, invasive arterial and central venous pressure, arterial oxygen saturation, end-tidal carbon dioxide concentration, temperature and urinary output were monitored throughout. The cumulative total dose of propofol administered was recorded every 1 h and the total infused noted at the end of surgery.

Blood samples were taken before operation and at 5 h after induction of anaesthesia and at 10 h when surgery was completed. These measurements were repeated at 24 h and 48 h after operation. This blood was assayed for hepatic glutathione-S-transferase using HEPKIT, an ELISA method from Biotrin International, Dublin. Samples were batched together to reduce assay variability.

Indocyanine green clearance was measured at similar times. Single injections (0.5 mg kg^{-1}) were

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TABLE I. *Plasma glutathione S-transferase activity after prolonged anaesthesia with propofol (mean (SD)). Normal range 0.75–6.0 ng litre*$^{-1}$

Time of measurement	GST activity (ng ml^{-1})
Baseline	2.51 (2.00)
5 h	2.64 (1.56)
10 h	2.0 (1.72)
24 h	1.41 (1.39)
48 h	1.04 (0.68)

used to evaluate hepatic uptake. Clearance was calculated from serum dye concentrations obtained at baseline and at 5, 10, 15 and 20 min after injection of indocyanine green into a large forearm vein. These samples were centrifuged and their optical densities determined at 805 nm using the patient's normal serum as a blank. Percentage disappearance rate (PDR) was calculated using the formula:

$$\mathrm{PDR} = \frac{0.693}{T_{\frac{1}{2}}} \times 100$$

where $T_{\frac{1}{2}}$ = the elimination half-life of ICG.

All values are expressed as mean (SD). The data were subjected to repeated measures analysis of variance. Statistical significance was inferred at $P < 0.05$.

The mean duration of anaesthesia was 10.1 h, and the dose of propofol given during this period ranged between 400 and 610 ml (mean 554.6 ml).

GST values did not exceed the normal range in any sample from any patient (table I).

Disappearance of indocyanine green at 5, 10, 24 and 48 h was expressed as a percentage change from baseline. After 5 h of anaesthesia, there was a 7.5 % reduction in the disappearance rate of ICG (NS) and at 10 h this reduction had decreased to 3.7 % (NS). Values calculated at 24 and 48 h showed no change from baseline.

COMMENT

Propofol, with its attractive pharmacokinetic profile, is used to maintain anaesthesia by continuous infusion. This study has examined the effects of a prolonged infusion of propofol on indocyanine green extraction and on a specific test of hepatic function.

Robinson and Patterson have outlined the effects of propofol on the commonly available liver function tests in patients undergoing *minor* surgery [4]. In their study, there were no major changes in liver enzyme activities. There is considerable doubt, however, regarding the usefulness and validity of standard liver function analyses in assessing hepatic injury from inhalation or i.v. anaesthetic agents.

The glutathione S-transferases are a complex group of enzymes that provide alternatives to measurement of plasma aminotransferase activity for detection of liver damage. The physical and chemical properties of GST are such that measurement of GST concentrations in plasma provides a very sensitive index of hepatic injury. When immunological methods are used to measure individual GST isoenzymes, it is possible to obtain considerable organ specificity. These advantages make the value of GST measurements particularly relevant in the clinical investigation of drug-induced liver damage.

Recent work has established the clinical benefits of GST measurement in assessing anaesthetic-induced liver injury during both brief and prolonged procedures [1, 2].

The rate of removal of the bolus doses of ICG from plasma, although subject to small errors, is adequate to detect changes in individuals. This has been validated recently by Cowan and colleagues, who demonstrated good agreement between measurements of hepatic perfusion from the peripheral disappearance curve alone and those that included hepatic vein catheterization [5].

Although propofol infusions have been shown to alter the extraction of some drugs, the small decreases in ICG clearance shown in this study may reflect the relaxant effects of propofol on smooth muscle which have been reported recently in isolated hepatic portal veins [6].

These data demonstrate that propofol, at a steady infusion rate of 6 mg kg^{-1} h^{-1}, has no significant effects on the extraction rate of ICG during prolonged anaesthesia and causes no increase in GST activity greater than the upper limit of normal (6 ng litre^{-1}). In view of the sensitivity, but particularly the specificity of this isoenzyme assay, we can be certain that, in the selected group of patients who were studied, there was no suggestion of hepatotoxic effect of the propofol used for induction and maintenance of prolonged anaesthesia.

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CASE REPORTS

APPARENT PACEMAKER FAILURE CAUSED BY ACTIVATION OF VENTRICULAR THRESHOLD TEST BY A MAGNETIC INSTRUMENT MAT DURING GENERAL ANAESTHESIA

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SUMMARY

A patient with a permanent pacemaker underwent radical neck dissection. After induction of anaesthesia, a magnetic surgical instrument mat was placed over the patient's chest. This caused the pacemaker to go into a threshold test which included a 2.5-s period of asystole. Surgery had to be abandoned temporarily. We suggest that magnetic instrument mats should not be used with pacemaker patients; not all pacemakers are converted to a fixed magnetic rate by application of a magnet. The anaesthetist should check to see if the patient has a pacemaker with a threshold test and, if possible, this should be rendered inactive. (Br. J. Anaesth. 1992; **69**: 645–646)

KEY WORDS

Complications: pacemaker failure. Heart: artificial pacemaker. Equipment: surgical.

CASE REPORT

An 82-yr-old man was admitted to hospital for radical right neck dissection of a metastasized carcinoma of the tongue. He had previously had a pacemaker implanted in October 1983 for complete heart block. The pacemaker was changed in April 1987 for a Siemans–Elema 688 which was programmed VVI at a demand rate of 70 beat min^{-1}. He remained asymptomatic, with normal exercise tolerance, without medication. The pacemaker was checked regularly. In March 1991, he presented with a squamous cell carcinoma of the tongue and underwent two uneventful anaesthetics for insertion and removal of irridium wires.

The patient was reviewed before operation by a cardiologist; a recent pacemaker check had shown no abnormality. History and examination were unremarkable. Full blood count, serum urea and electrolyte concentrations, and ECG were within normal limits. Premedication comprised morphine 5 mg and atropine 0.4 mg. 22-Gauge radial arterial and 16-gauge venous cannulae were inserted and ECG, end-tidal carbon dioxide and arterial oxygen saturation monitored (Datex Cardiocap). Anaesthesia was induced with thiopentone 200 mg and morphine 5 mg followed by atracurium 50 mg. The trachea was intubated with a 9.0-mm tracheal tube and the lungs ventilated with a Nuffield Penlon 200 ventilator via a Mapleson D (Bain) breathing system with nitrous oxide and 1% isoflurane in oxygen. Unknown to the anaesthetist, a magnetic surgical instrument mat (Applied Research Ltd) was placed over the patient's left chest. Before surgery could begin, an abnormal rhythm appeared on the ECG (fig. 1). From a paced rhythm of 70 beat min^{-1} the pacemaker increased to 99 beat min^{-1} for 16 beats and then to 119 beat min^{-1} for 11 beats, became asystolic for 2.5 s and then repeated the cycle. During the asystolic period, there was no cardiac output evident from the arterial pressure recording. Several episodes of bradycardia were noted also. The sudden onset of this rhythm caused the anaesthetist to abandon surgery; the patient was de-towelled and normal paced rhythm returned. At this time, the magnetic mat was brought to the attention of the anaesthetist. A cardiologist was consulted and he rechecked pacemaker function. Surgery then proceeded uneventfully without the mat in place.

DISCUSSION

The dangers of using magnetic instrument mats on patients with a pacemaker have not been reported previously.

The application of a magnet to permanent pacemakers does not always result in the pacemaker going into a fixed rate, as is commonly thought [1]. As noted previously [2–4], it is essential that anaesthetists understand exactly what type of pacemaker a patient has and what pacing modes they may expect.

Usually, a programmer is needed to test the stimulation threshold of most programmable pacemakers. In order to determine the stimulation threshold that captures the myocardium, the output voltage is reduced gradually until capture is lost. This threshold is a test of the integrity of the pacing lead and the electrode–myocardial interface and it may be influenced by cellular factors, such as serum

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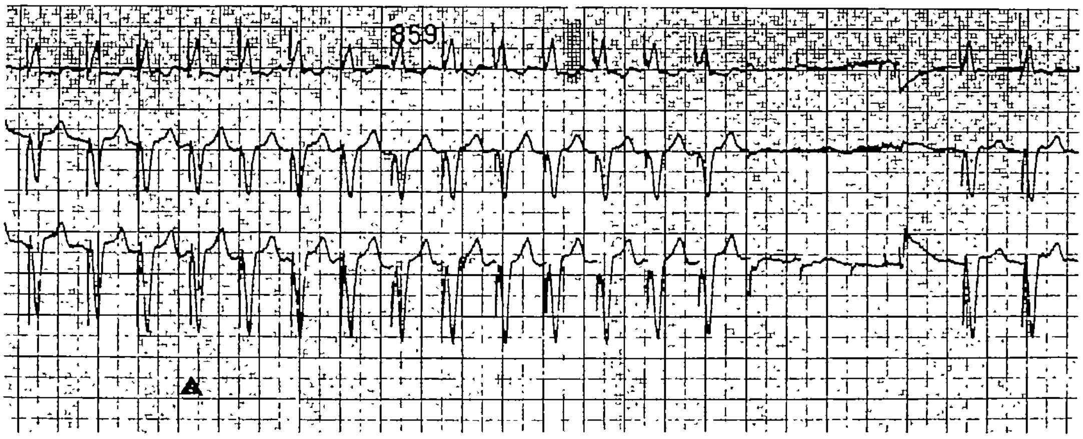

FIG. 1. ECG leads 1, 2 and 3. The 16 pulses of the threshold test start from ▲. There is loss of capture at pulse 4. After the O-V pulse, the rhythm returns to 16 pulses at the magnetic rate of 99 beat min^{-1}.

potassium concentration [5, 6], oxygen partial pressure [7], acid–base status [8], antiarrhythmic agents [9] and physical factors such as lead and insulation fracture in addition to oedema and tissue growth around the electrode which can be modified by defibrillation [10, 11], surgical diathermy [12] and myocardial infarction. However, in all Siemens programmable pacemakers and in the older versions of Telectronic pacemakers (Optima MP and MPT), the threshold function mode may be activated by a normal magnet unless this function has been programmed to be inactive. The reason for this is to allow the pacemaker threshold to be checked in the absence of a programmer, as may be the case in less sophisticated clinics.

When a magnet is placed near the pacemaker of a Siemens model, the "Vario" cyclic test sequence occurs (Siemens–Elema 688 Manual). This comprises a battery test phase (as seen in all other pacemakers) and a threshold test phase, and this sequence is repeated for as long as the magnet is present. The battery phase consists of 16 pulses with constant amplitude at 99 beat min^{-1}, followed immediately by the threshold test in which the amplitude of the pulses is reduced gradually in 15 steps from the maximal programmed amplitude to zero. The rate is 119 beat min^{-1} and the test is terminated by the O-V pulse. The programmed amplitudes can be 10, 5 or 2.5 V, with the smallest voltage giving the longest battery life of up to 18 yr.

Unfortunately, no ECG recordings were made during operation, therefore the patient was rechallenged with the mat in the pacemaker clinic (fig. 1). The stimulation threshold was calculated at 1.33 V (the maximal amplitude was 5 V), which is obviously fairly small, but if the stimulation threshold had been substantially greater, the period of asystole would have been prolonged and may have led to significant cerebral ischaemia.

The episodes of bradycardia noted in our patient are more difficult to explain and could not be reproduced on rechallenging. However, it has been described that waving of a magnet over some VVI pacemakers can cause prolonged inhibition as a result of changing magnetic fields which are sensed, with consequent inhibition of pacemaker output [13].

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EXTRADURAL ABSCESS COMPLICATING EXTRADURAL ANAESTHESIA FOR CAESAREAN SECTION

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SUMMARY

Extradural abscess has been described infrequently as a complication of extradural anaesthesia and analgesia. We describe an abscess that developed 5 days after operation in a patient who had extradural anaesthesia for Caesarean section and postoperative analgesia, and review the literature on extradural abscess complicating extradural catheterization, including a discussion on pathogenesis, clinical presentation, diagnosis and management. There have now been 16 reported cases of extradural catheter-related extradural abscess. Only one previous case has been in obstetric practice, despite the widespread use of these techniques in this specialty. A disproportionate number of cases have involved thoracic catheters. Duration of catheterization ranged from 40 h to 6 weeks, the majority of catheters being in place for 5 days or less. The time from catheter placement to development of symptoms ranged from 72 h to 5 months. The causative organism was isolated in 11 cases: Staphylococcus aureus *was identified in nine (82%) and* Staphylococcus epidermidis *in two (18%). Outcome was reported in 15 cases, of which seven (47%) had a full or near full recovery and eight (53%) had a persistent neurological deficit. One case was managed successfully without surgery. Fifty percent of all cases have been reported in the past 5 years. With the increasing use of extradural techniques for anaesthesia and analgesia, this serious complication may be seen more frequently in the future.* (Br. J. Anaesth. 1992; **69**: 647–652)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural. Complications: extradural abscess.

CASE REPORT

A 26-yr-old, 80-kg woman presented for Caesarean section at 34 weeks gestation. She was in early labour with a twin pregnancy and a footling breech. The pregnancy had been complicated by mild pre-eclampsia, but platelet count and coagulation profile were normal. She had a past history of mild, non-incapacitating back pain and penicillin allergy.

Extradural anaesthesia was performed by the on-call anaesthetic registrar who scrubbed with 7.5% povidone-iodine (Betadine) and donned sterile gown and gloves, mask and cap. The patient's back was disinfected using 1% iodine in spirit. After skin infiltration with 1% lignocaine, an attempt was made to locate the extradural space at the L2–3 interspace using a 16-gauge disposable Tuohy needle. After two needle insertions struck bone, this interspace was abandoned and another attempt was made using the same needle at the L3–4 interspace. Here, the extradural space was located at 7 cm depth and a catheter inserted 5 cm into the space. The puncture site was covered with a folded sterile gauze square and a transparent dressing (Tagaderm, 3M). A test dose of 1.5% lignocaine 3 ml in 7.5% glucose with adrenaline 15 μg was administered via the catheter. Anaesthesia to T4 was produced using 18 ml of a solution made by adding 8.4% sodium bicarbonate 2 ml and adrenaline 100 μg to 2% lignocaine 20 ml. A dose of 50 mg of preservative-free pethidine was also administrated extradurally. All drugs were believed to be sterile, drawn from single-use ampoules, and delivered via a 0.2-μm bacterial filter (Portex). Surgery was uneventful. Prophylactic antibiotics were not administered.

As is standard practice in our institution, the extradural catheter was left *in situ* for the delivery of postoperative analgesia. This consisted of intermittent 10-ml doses of 0.5% sterile, preservative-free pethidine drawn from single-use ampoules and injected through the filter, which was capped between doses. A total of 14 doses was given before the catheter was removed 50 h postpartum.

The patient remained well until the 5th day after operation when she developed low back pain, a fluctuating fever that spiked to 39.5 °C and rigors. She was noted to have "offensive appearing" lochia and there was tenderness, bruising and a pustular lesion at the extradural site. A provisional diagnosis of endometritis was made. Blood cultures, a high vaginal swab and a swab from the extradural site were taken and i.v. cefuroxime 750 mg 8-hourly was commenced. Her back pain increased and by the 7th day after operation she had pain radiating to her legs

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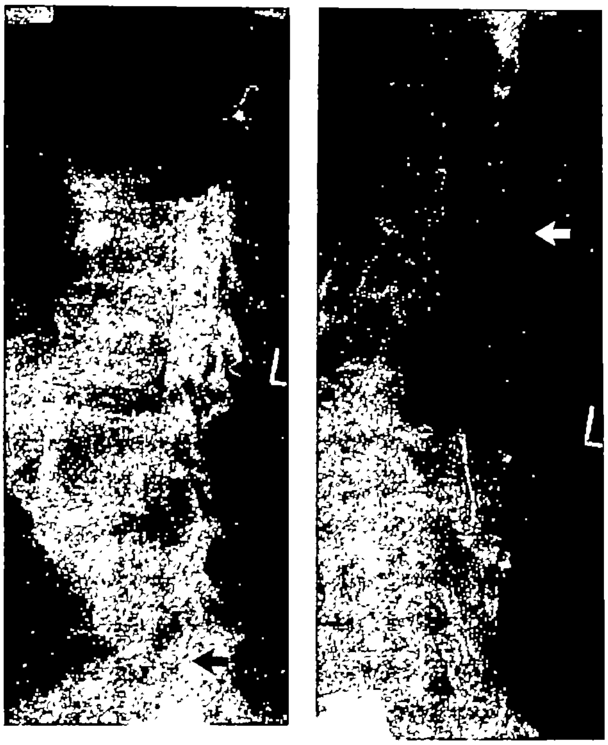

FIG. 1. Myelogram showing complete block to contrast flow at T12 (arrows).

and feet and experienced difficulty with weight bearing. Her white cell count was increased to 26.9×10^9 litre^{-1} and her temperature fluctuated between 36.4 and 37.6 °C. Neurological examination was normal at this time.

During the next day, the patient developed paraesthesia and weakness of both legs and had difficulty passing urine. Her temperature increased to 38.4 °C and she had absent ankle jerks and diminished sensation to pinprick from S1 to S5 on the left and from L4 to S5 on the right. Results from the high vaginal swab showed normal commensals, but the blood cultures grew *Staphylococcus aureus* resistant to penicillin and sensitive to flucloxacillin. She was referred to the neurosurgical team for urgent investigation. A myelogram was performed via a lateral C1–2 puncture and showed a complete block to contrast at T12 (fig. 1). Laminectomy was performed and an extradural abscess extending to the left paravertebral muscle was identified and drained. Culture of this pus subsequently grew *Staphylococcus aureus*. Antibiotic therapy was changed to a combination of i.v. cefotaxime 1 g 6-hourly, continued for 12 days, together with oral rifampicin 450 mg 12-hourly, continued for 4 weeks. Recovery was hindered by persistent radicular pain, but this improved gradually and, when reviewed 8 weeks after operation, the patient had made a full recovery.

Bacteriophage typing of the staphylococcal isolate from blood and abscess was performed and both isolates had identical typing patterns. The isolate from the extradural site was not available for typing. At the 8-week follow up, nasal and perineal swabs taken from the patient both grew *Staphylococcus aureus*, but of a phage type different from that found in the abscess. *Staphylococcus aureus* was not isolated from swabs taken from the skin surrounding the operative site. The anaesthetist who had inserted the extradural catheter was screened for staphylococci at the same time, but nasal and perineal swabs did not yield *Staphylococcus aureus*. Routine sterility testing of extradural test doses over the past 2 years has not identified contaminated batches.

DISCUSSION

Infection of the extradural space is a recognized, albeit rare, complication of extradural anaesthesia and analgesia. Extradural abscess complicating extradural catheterization was first reported in 1974 [1, 2]. A search of the literature has identified 15 further cases, of which only one has been in obstetric practice [3–14] (table I). Fistula formation after extradural catheterization has also been described [15], and extradural abscess has occurred after single-shot extradural injections [16, 17], caudal extradural anaesthesia [18] and spinal anaesthesia [19–21]. Extradural abscess unrelated to anaesthesia is well reported, with an estimated incidence of 0.2–1.2 per 10000 hospital admissions [3].

In obstetric practice, extradural anaesthesia with or without the use of catheters is used extensively for pain relief and operative obstetrics and has a low incidence of serious complications [10, 22, 23]. Infections of the extradural space are rare, despite the difficulties of performing techniques aseptically on the labour bed [8]. In a retrospective study carried out by postal questionnaire of serious, non-fatal complications associated with extradural blocks in obstetrics, Scott and Hibbard found only one case of extradural abscess in 505000 extradural blocks performed in the U.K. from 1982 to 1986 [10]. Fatal extradural abscess has occurred after continuous caudal extradural analgesia in labour [18]. Other infective complications of extradural anaesthesia in obstetrics have included non-abscess infection of the extradural space [24] and meningitis [25]. Meningitis has also been described after spinal anaesthesia in obstetrics [26, 27].

Infection of the extradural space may occur by several mechanisms after extradural anaesthesia [17]. First, organisms may be introduced directly during needle or catheter insertion. This mechanism has been implicated in one case in which the infecting organism was later isolated from nasal swabs taken from the anaesthetist [4]. Second, infection may occur after injection of contaminated fluid, as has occurred with the use of multidose vials [4]. Third, spread may occur directly from an adjacent area of infection [28]. Fourth, infection may be indirect via haematogenous spread from a distant focus of infection [2, 24].

The incidence of contamination of extradural catheters has been reported to be as great as 22% [29]; however, the incidence of clinically apparent infections is remarkably small. The reasons why some cases manifest as abscesses are unclear. The majority of cases of catheter-associated extradural abscess have involved catheters in place for 5 days or less, therefore a long duration of catheterization is

TABLE I. *Extradural abscesses associated with extradural catheterization*

Reference	Extradural site	Indication	Extradural drugs used	Duration of catheterization	Time after insertion to significant symptoms	Infecting organism	Outcome	Comments
[1], [2]	Thoracic	Postoperative analgesia	Local anaesthetics	40 h	4 days	*Staphylococcus aureus*	Mild sensory deficit	Same case reported twice
[3]	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	
[4]	A: Lumbar	Priapism	Local anaesthetic	72 h	10 days	*Staphylococcus aureus*	Full recovery	A: Contaminated drug vial used
	B: Thoracic	Rib fractures	Local anaesthetic	4 days	4 days	*Staphylococcus aureus*	Sensory impairment	B: Causative organism isolated from anaesthetist
[5]	Thoracic	Rib fractures	Morphine	80 h	20 days	*Staphylococcus aureus*	Weakness, urinary retention	
[6]	Lumbar	Knee surgery	Not specified	4 days	2–3 weeks	*Staphylococcus epidermidis*	Near full recovery	
[7]	Lumbar	Peripheral vascular disease	Not specified	6 weeks	5 months	Not specified	Persistent pain	Patient with diabetes and chronic renal failure
[8]	Thoracic	Chronic pain	Local anaesthetic Fentanyl	72 h	72 h	Not specified	Paraesthesiae, back spasms	
[9]	Lumbar	Rib fractures	Local anaesthetic Morphine	13 days	12 days	*Staphylococcus aureus*	Full recovery	
[10]	Not specified	Obstetrics	Not specified	Not specified	Not specified	Not specified	Incomplete recovery	
[11]	Thoracic	Postoperative analgesia	Local anaesthetic Fentanyl	96 h	12 days	*Staphylococcus aureus*	Weakness, urinary retention	Patient with cancer
[12]	Lumbar	Cancer pain	Morphine	4 weeks	4 weeks	*Staphylococcus epidermidis*	Full recovery	Patient with cancer Treated non-surgically
[13]	A: Thoracic	Herpes zoster	Local anaesthetic Steroid	1st: 36 h 2nd: 3 days	31 days (after 1st catheter)	*Staphylococcus aureus*	Full recovery	A. Patient with herpes zoster. Extradural steroids given
	B: Cervical	Reflex sympathetic dystrophy	Local anaesthetic	1st: 5 days 2nd: 5 days	7 weeks (after 1st catheter)	None identified	Full recovery	B. Patient on oral steroids
[14]	Thoracic	Perioperative analgesia	Local anaesthesia Fentanyl	5 days	28 days	*Staphylococcus aureus*	Paraplegia, urinary retention	Patient with rheumatoid arthritis I.m. steroids given
Present report	Lumbar	Caesarean section	Local anaesthetic Pethidine	50 h	5 days	*Staphylococcus aureus*	Full recovery	

not necessary. The site of insertion of catheters does appear to be significant; of the 16 reported cases, seven (44 %) involved thoracic catheters, six (38 %) involved lumbar catheters, and one case (6 %) involved cervical extradural catheterization; the site of catheterization was not specified in two cases (table I). This indicates a disproportionately high involvement of thoracic catheters, considering that in most practices lumbar placement is far more frequent than thoracic. It may reflect the relative difficulty locating the thoracic extradural space compared with the lumber space [30]. Insertions that are difficult are more likely to be traumatic, and may result in a greater incidence of extradural haematoma, which could then act as a nidus for infection [2, 20, 24]. Breaks in aseptic technique may also be more likely when insertion is difficult.

In our patient, the source and route of infection remain unclear. Full aseptic precautions were taken during catheter insertion and the infecting organism was not isolated from the anaesthetist. Extradural analgesics were delivered in the ward by intermittent bolus doses, rather than by continuous infusion, through a closed delivery system as has been recommended [31, 32]. However, all drugs were believed sterile, were freshly drawn from single-use ampoules and injected using sterile, single-use syringes attached directly to a bacterial filter. Extradural insertion in this patient was difficult, involving multiple needle insertions, which may have made contamination during insertion more likely or may have predisposed to extradural haematoma formation. Although the *Staphylococcus aureus* grown from the pustular lesion on the patient's back was not phage-typed, it is likely to be the same as that isolated from the blood and abscess; the pustule may have been the result of concurrent infection, or the source of spread to the extradural space. Spread may have occurred haematogenously, blood cultures having been positive, or by direct spread along the catheter or needle track.

The most common causative organism in extradural abscess unrelated to anaesthesia is *Staphylococcus aureus* [3, 28, 33–35], although recent reviews suggest the spectrum of causative organisms is broadening [28, 35]. *Staphylococcus aureus* has also been the commonest infecting organism in catheter-associated cases, identified in nine (82 %) of 11 cases in which an organism was isolated, with *Staphylococcus epidermidis* identified in two (18 %) (table I).

The clinical features of extradural abscess were described by Rankin and Flothow in 1946 [36] and by Heusner in 1948 [37]. Four stages are described: spinal ache, nerve root pain, weakness and paralysis. Associated findings may include fever, leucocytosis, increased erythrocyte sedimentation rate, alterations in reflexes, neck stiffness and headache [28, 34]. Positive blood cultures correlating with culture results from the abscess are found in about 25 % of cases [28]. The cerebrospinal fluid is almost always abnormal [33], but lumbar puncture carries the risk of neurological deterioration if performed below a complete spinal block [38], and meningitis may follow if the needle traverses the abscess [34].

Extradural abscess may have a highly variable presentation which can make diagnosis difficult [33]. A review of 29 non-catheter-related cases found all patients had spinal pain at presentation, but only 69 % had a new neurological deficit and only 62 % had an increased temperature [35]. Conversely, in one case which followed extradural catheterization, the patient presented with sensory deficit and paralysis in the absence of pain [5]. In our patient, there was a significant delay in diagnosis, owing to the initial lack of localizing neurological signs. Symptoms in catheter-associated cases have occurred at varying times after placement of the catheter, ranging from 72 h to 5 months. Delayed presentation may make diagnosis difficult. One patient developed symptoms of spinal cord compression 20 days after removal of an extradural catheter and only had a diagnosis of extradural abscess made after laminectomy had been performed [14]. Patients with extradural catheters inserted for treatment of chronic pain may also present diagnostic problems. In these patients, the development of pain from the abscess may be difficult to separate from the patient's chronic condition [8].

The mainstay of diagnosis of extradural abscess lies in radiological imaging [34], with myelography currently being the main diagnostic tool [28, 33, 35]. Several reports have shown the usefulness of magnetic resonance imaging (MRI), which eliminates the need for dural puncture [39–41], and has been used successfully in a patient allergic to contrast material [42]. However, MRI cannot distinguish between frank pus and granulation tissue [34] and may not diagnose the extent or presence of an abscess in patients with associated meningitis [41]. Computed tomography (CT) has also proven useful [43] and may be combined with myelography. However, definitive diagnosis may not be possible with CT alone [40]; in one report, the initial CT was positive in only three of nine patients with a subsequently proven diagnosis of extradural abscess [33].

The management of extradural abscess consists of early diagnosis, surgical exploration and drainage, and appropriate antibiotics [33, 34, 37, 44]. There have been reports of patients managed successfully without surgery [13, 33, 43, 45–47], but medical management carries a significant risk and non-operative treatment should be considered only for patients with a very high operative risk [34]. Outcome is related to the duration of time the abscess has been present, and the degree of neurological impairment, at the time of definitive surgical treatment [28, 33, 44]. Delay in diagnosis and treatment may result in permanent neurological damage [37, 48]. Of the 16 catheter-related cases, 14 underwent surgery and one patient in whom an early diagnosis was made was managed successfully with antibiotics [12]. Management not specified in one case. Outcome was reported in 15 cases of which seven (47 %) had a full or near full recovery and eight (53 %) had a persistent neurological deficit, ranging from mild sensory impairment to paraplegia and urinary retention (table I).

Many reported cases of extradural abscess associated with extradural anaesthesia have had identifiable risk factors such as diabetes [7], chronic renal failure [7], cancer [11, 12], steroid administration [13, 14, 16, 17], herpes zoster [13] and rheumatoid arthritis [14] that may have predisposed to susceptibility to infection [49–51]. The obstetric patient is usually young, healthy and without these risk factors. Nonetheless, there has been an increasing trend towards extradural anaesthesia and analgesia in obstetrics and in other specialties, and the practice of placing catheters in the extradural space for management of acute, chronic and postoperative pain is becoming increasingly popular. Fifty percent of all cases of extradural abscess complicating extradural catheterization have been reported in the past 5 years: it appears this rare complication is becoming more common. Therefore, it is essential that the anaesthetist is meticulous in ensuring a strict aseptic technique, taking particular care when placing catheters in the thoracic space or in the debilitated or immunocompromised patient. All medical staff should be aware of the possibility of this complication. Early diagnosis of extradural abscess will be facilitated by a high index of suspicion. It should be considered in any patient who has had an extradural catheter *in situ* and demonstrates systemic signs of infection or significant back pain. The occurrence of radicular pain, weakness, paralysis or bladder dysfunction are indications for immediate neurosurgical referral and specialized investigations.

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GENERAL ANAESTHESIA AND THE HYPEREOSINOPHILIC SYNDROME: SEVERE POSTOPERATIVE COMPLICATIONS IN TWO PATIENTS

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SUMMARY

Two patients with markedly increased eosinophil counts developed severe postoperative complications after general anaesthesia. One patient suffered life-threatening Adult Respiratory Distress Syndrome (ARDS), while the other presented with a coagulopathy and less severe respiratory problems. The hypereosinophilic syndrome is described and the possibility of a role of eosinophils in the pathogenesis of tissue injury is discussed. These cases suggest that, in patients with marked eosinophilia requiring general anaesthesia, perioperative steroid cover is advisable. This may reduce or prevent serious lung damage and other complications. (Br. J. Anaesth. 1992; **69**: 653–656)

KEY WORDS

Anaesthesia: general. Complications: hypereosinophilic syndrome. Lung: ARDS.

We describe two patients who developed severe postoperative complications in association with very high eosinophil counts. The problems had not been anticipated in view of the absence of pre-existing pathology and the type of surgery involved. These cases highlight the potential for eosinophils to cause tissue injury and raise the possibility of their involvement in the pathogenesis of the Adult Respiratory Distress Syndrome.

CASE REPORTS

Patient No. 1

A 14-yr-old schoolboy was referred for investigation of hepatosplenomegaly and eosinophilia. He gave a 7-week history of watery diarrhoea, malaise, anorexia and weight loss. He was thin, with a few enlarged cervical lymph nodes and three discrete necrotic skin lesions. Marked hepatosplenomegaly was found, but the remainder of the examination was normal. Investigations revealed: haemoglobin 11.5 g dl^{-1}, WBC 63×10^9 $litre^{-1}$ (34% eosinophils, 47% neutrophils, 11% lymphocytes, 8% monocytes), platelets 300×10^9 $litre^{-1}$. Serum urea and electrolyte concentrations were normal: alkaline phosphatase 323 iu $litre^{-1}$, alanine transferase 57 u $litre^{-1}$, total protein 102 g $litre^{-1}$, albumin 22 g $litre^{-1}$. The chest radiograph was normal on admission. Abdominal ultrasound confirmed a greatly enlarged liver of homogenous texture and showed chains of enlarged para-aortic and pericaval lymph nodes. A provisional diagnosis of myeloproliferative disease or lymphoma was made and it was decided to proceed to insertion of a Hickman line, posterior iliac crest bone marrow aspirate and liver biopsy under general anaesthesia.

The anaesthetic technique consisted of premedication with temazepam and metoclopramide, induction with fentanyl 4 $\mu g\ kg^{-1}$, propofol 2 $mg\ kg^{-1}$ and atracurium 0.7 $mg\ kg^{-1}$ before intubation, maintenance with nitrous oxide–oxygen–isoflurane, increments of atracurium and IPPV. The inspired oxygen fractional concentration was 0.35 and the arterial oxygen saturation measured by pulse oximetry was 100% throughout. The procedure was uneventful.

In the hours after the operation, the patient became pyrexial (39 °C) and tachypnoeic with a dry cough. Auscultation of the chest was normal and there was no other clinical sign of infection. Gentamicin and azlocillin were commenced empirically. Twenty-four hours later, the tachypnoea had worsened (50 b.p.m.) and he was cyanosed whilst breathing air. The chest radiograph on the first day after operation showed widespread alveolar shadowing. He was hypoxaemic and anaemic with a haemoglobin concentration of 7.8 g dl^{-1}. The differential diagnosis lay between opportunistic infection and eosinophilic pulmonary infiltration. Sputum cultures for acid fast bacilli, bacterial and atypical pathogens were performed. Blood and stool cultures and antibody screens were also undertaken. The bone marrow was hypercellular with marked eosinophilia, although maturation was normal. Liver biopsy showed inflammation in the portal zones with piecemeal necrosis, polymorph infiltration and fibrosis. There was no sign of arteritis in the specimen. The blood film showed increased de-

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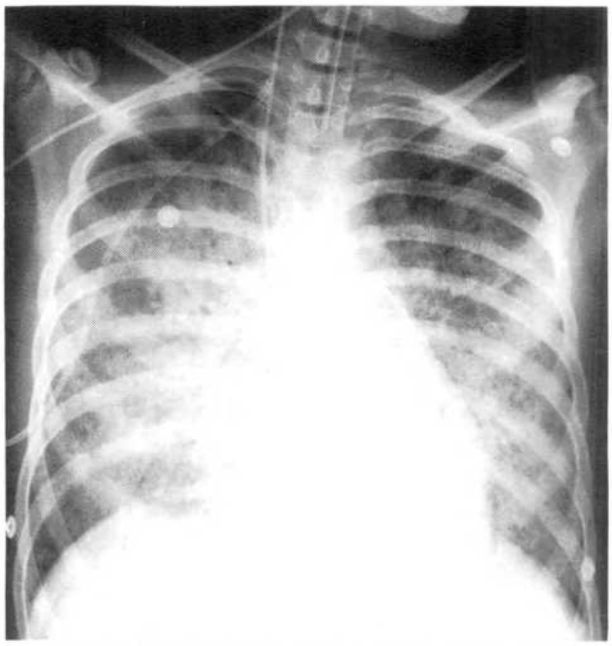

FIG. 1. Patient No. 1: Chest radiograph of the patient on the third day after operation, showing the classical infiltrates of the Adult Respiratory Distress Syndrome.

granulation of circulating eosinophils: the number of degranulated eosinophils increased from 13.25×10^9 litre^{-1} before operation to 17.1×10^9 litre^{-1} after operation (a 29% increase), with no change in the total white cell count. Erythromycin and i.v. hydrocortisone 100 mg 6-hourly were added to the drug regimen.

The patient later developed bilateral fine basal inspiratory crepitations with worsening hypoxaemia and exhaustion. Severe Adult Respiratory Distress Syndrome (ARDS) was diagnosed and 48 h after operation he required mechanical ventilation. An $F\mathrm{I}_{O_2}$ of 1, tidal volume 20 ml kg^{-1} and PEEP of 15 cm H_2O were needed to maintain the arterial oxygen saturation between 85 and 90%. Blood-stained, frothy sputum was aspirated from the tracheal tube. Increased airway tone and reactivity were manifested by widespread bronchospasm and increased inflation pressures requiring nebulized salbutamol. Pulmonary artery catheter pressures (right ventricular 33/0 mm Hg, pulmonary artery 30/15 mm Hg, pulmonary capillary wedge pressure 14/3 mean 5 mm Hg), were consistent with non-cardiogenic pulmonary oedema (fig. 1). He was shocked and oliguric, requiring frequent colloid infusion and inotropic support. Blood cultures remained negative. I.v. methyl prednisolone was started because of the continued increase in the eosinophil count (WBC 110×10^9 litre^{-1}, eosinophils 56×10^9 litre^{-1}) on the third day after operation.

Subsequently, the patient's condition began to improve; he became apyrexial and ventilatory and oxygen requirements decreased. Recovery was complicated by Klebsiella septicaemia and necrotizing pneumonia resulting in massive cystic lung lesions and recurrent tension pneumothoraces. The trachea was extubated after 21 days in Intensive Care. The total white cell count and eosinophil count had decreased and the dose of steroids was gradually reduced. His exercise tolerance was severely limited because of large emphysematous bullae compressing the remaining lung tissue. Slow improvement continued and he was discharged on the 47th day, receiving prednisolone 15 mg daily, his eosinophil count having decreased to zero. An echocardiogram performed before discharge showed hyperechogenic areas within the myocardium, consistent with eosinophilic "microabscesses". Valvular function was normal. Investigations for viral, parasitic and opportunistic infections remained negative. Electrophoresis of serum proteins before discharge showed a slight increase in α_2 globulins with total proteins 65 g litre^{-1} and albumin 32 g litre^{-1}.

Six weeks later, the patient's spleen and liver were no longer palpable and there was no lymphadenopathy. His exercise tolerance was improving. The eosinophil count continued to fluctuate over the following 9 months and was controlled with varying doses of oral prednisolone and intermittent i.v. vincristine. Thereafter, the eosinophil count returned to normal and during 3 years follow up he has remained well apart from minor bowel upset controlled by low dose prednisolone. The possibility of an underlying myeloproliferative disorder such as chronic granulocytic leukaemia has not been excluded by repeat bone marrow and chromosome analysis, but the prolonged normal peripheral blood count and the clinical course make this diagnosis unlikely.

Patient No. 2

A 52-yr-old man was admitted complaining of epigastric pain, nausea and vomiting. He had no significant past medical history and smoked 40 g of pipe tobacco per week. He was apyrexial, cardiorespiratory examination was unremarkable and he had guarding and rebound tenderness in the right iliac fossa. Investigations showed: Hb 14.6 g dl^{-1}, WBC 25.7×10^9 litre^{-1}, serum concentrations of urea, electrolytes and amylase normal. There was no clinical evidence of haemorrhagic tendency. The chest radiograph was clear. Appendectomy was planned for the same day.

He was premedicated with pethidine and atropine. A rapid sequence induction technique was used with thiopentone and suxamethonium. Anaesthesia was maintained with nitrous oxide, oxygen, halothane and intermittent boluses of alcuronium. Emergency appendectomy was carried out uneventfully. The specimen was macroscopically normal and histology was not requested.

Twelve hours after operation, there was considerable blood loss from the surgical wound, the patient developed tachycardia and hypotension and required blood transfusion. Further examination of the preoperative blood sample showed that 65% of WBC were eosinophils (16.75×10^9 litre^{-1}) and a platelet concentration of 16×10^9 litre^{-1}. The coagulation screen was normal. Platelet transfusion was carried out.

On the first day after operation, bone marrow aspiration yielded a sample with increased cellularity and 45% eosinophils, 10% at the eosinophil myelocyte stage. Megakaryocytes were reduced and platelet budding was scant. Possible diagnoses considered were a leukaemic disorder, advanced parasitic disease, polyarteritis nodosa and hypereosinophilic syndrome. Extensive investigations for parasitic infection, connective tissue disorders and other conditions associated with eosinophilia were negative.

On the second day after operation prednisolone 10 mg three times daily was commenced and further blood and platelet transfusions were required. On day 7, the patient was found to be tachypnoeic (ventilatory frequency 30 b.p.m.), tachycardic (160 beat min^{-1}) and centrally cyanosed. He was transferred to the Intensive Care Unit where he was given 100% oxygen by mask. Blood-gas analysis revealed a pH of 7.3, Pa_{O_2} 8.1 kPa, Pa_{CO_2} 4.2 kPa. The chest radiograph showed bilateral diffuse shadowing consistent with alveolar exudation. He was given i.v. hydrocortisone 100 mg four times daily. His respiratory status improved over 48 h and he was fit for transfer to a general ward. At this stage his platelet count began to improve and increased slowly to normal values during the next 5 weeks.

Whilst receiving steroid treatment, the patient required two further general anaesthetics for resuturing of abdominal wall dehiscence. Both procedures were uneventful. He was finally discharged 7 weeks after admission.

Over the next 5 years, he continued to have increases in his eosinophil count controlled with varying doses of prednisolone. He maintained a normal platelet count and at no time was there development of a leukaemic disorder or other condition associated with eosinophilia.

DISCUSSION

An increase in the total blood eosinophil count may occur in association with a large variety of conditions. Worldwide, the most important cause of eosinophilia is parasitic infection, but allergy, skin disease, neoplasia and drugs are common causes. The increase in cell numbers is usually mild or moderate. Occasionally, however, greatly increased counts (20–40 × 10^9 litre^{-1}) may be seen [1].

Although the eosinophil was identified by Ehrlich more than a century ago, its role in disease has been recognized only recently. It was assumed previously that eosinophils played a beneficial role in host defence against parasitic infections and in down-regulation of the inflammatory process after immediate-type hypersensitivity reactions. However, as the toxicity of the eosinophil to human tissue has become evident in the past decade, this cell is now increasingly regarded as a potent pro-inflammatory agent with considerable tissue-damaging potential and a mediator of epithelial injury and bronchial hyperreactivity [2]. It is also recognized as producing endomyocardial fibrosis in Loeffler's disease [3].

The hypereosinophilic syndrome was described first in 1968 by Hardy, who associated a range of complications with persistent eosinophilia [4]. The criteria for the hypereosinophilic syndrome (HES) were defined later by Chusid and colleagues [5] as: eosinophilia $> 2.5 \times 10^9$ litre^{-1}; persistent eosinophilia for at least 6 months unless fatal in the shorter term; organ involvement and dysfunction; no other recognizable cause of eosinophilia. The syndrome is rare, occurring more commonly in men than in women (male:female ratio 9:1) [1]. The mode of presentation is varied. Rarely (10%), it is an incidental finding. However, lung involvement is common, with cough, dyspnoea and pyrexia in up to 40% of cases [6]. ARDS complicating the hypereosinophilic syndrome has not previously been described.

Our first patient represents a severe form of the hypereosinophilic syndrome, with multiple system involvement, including lung, skin, gut, reticuloendothelial and cardiovascular systems, requiring 3 weeks of life support in Intensive Care. In the second patient, the part played by the very high eosinophil count in the postoperative respiratory complications was less clearly defined because of the associated thrombocytopenia. Decreased platelet counts have been reported in the hypereosinophilic syndrome [7]. Pulmonary capillary pressure was not measured in this patient and the pulmonary problem occurred several days after anaesthesia. Pulmonary haemorrhage, sepsis or fluid overload could have been responsible for the symptoms, but the rapid resolution of the respiratory distress following the start of high-dose parenteral steroids without diuretic or antimicrobial therapy supports the significant contribution of the eosinophilia.

The mechanism of tissue damage by eosinophils is related to the large intracytoplasmic granules which, when activated, release a variety of cytotoxic mediators. The most important of these are major basic protein (MBP), eosinophilic cationic protein (ECP), leukotriene C_4 and oxygen free radicals [2, 8]. There is also release of a variety of enzymes, including collagenase and lecithinase. An important finding in HES is vacuolation and degranulation of the circulating eosinophils, whereas bone marrow eosinophils in these patients do not show such changes. It is proposed that both the normal effector mechanisms of eosinophils in parasitic infections and the tissue damage induced in HES are secondary to peripheral degranulation with release of MBP and other mediators [8]. Indeed, the presence of vacuolation has been correlated with the extent of tissue damage [6]. In patient No. 1 reported here, the number of degranulated circulating eosinophils increased by 29% after operation. Ayars and colleagues have shown that activated eosinophils can provoke detachment type injury at the pneumocyte layer of the alveolar membrane. This causes membrane breakdown, with efflux of cells and proteins into the alveolus, leading to low pressure pulmonary oedema [9]. Moreover, Hallgren and co-workers have demonstrated markedly increased concentrations of ECP in both serum and bronchoalveolar lavage fluid in patients with ARDS, while the concentration of ECP correlated with the severity of ARDS [10]. Recently, eosinophils have been shown experimentally to increase vascular permeability and resistance in isolated rat lungs [11, 12] and ECP is known to cause increase airways reactivity and tone

[13]. Our first patient presented with both increased pulmonary vascular permeability and severe bronchospasm. We suggest that this patient's respiratory problems were associated with lung damage produced by eosinophil degranulation. In the second patient, respiratory failure could have been precipitated by various causes but, in our opinion, eosinophils most probably played a part. These patients illustrate how eosinophil-mediated damage may represent an alternative mechanism to the well established neutrophil-mediated pathway [14, 15] in the pathophysiology of the Adult Respiratory Distress Syndrome.

The mainstay of treatment in the hypereosinophilic syndrome is steroids. These drugs inhibit eosinophil chemotaxis, adherence and degranulation, thus preventing the release of cytotoxic mediators. In addition, they gradually deplete the marrow of eosinophil reserves. The use of steroids in the treatment of ARDS is still controversial. In the past few years they have been considered unhelpful and to increase the risk of infection [16]; however, recent reports have demonstrated a possible beneficial effect of steroids in this syndrome [17]. The role of steroids in septic states is equally unclear, despite two recent randomized controlled trials on this subject [18, 19]. In these trials, no overall reduction in mortality was demonstrated in the steroid-treated patients, although patients with gram-negative sepsis treated with steroids had a better prognosis. Steroids, however, tended to increase the incidence of secondary infections in all patients. In the two patients reported here, steroid treatment promoted relatively rapid recovery of the severe respiratory symptoms, but the first case was complicated by serious secondary infection. Steroids are not always successful in the treatment of HES. Vincristine and hydroxyurea have proven useful in aggressive disease [7]. Our first patient was controlled successfully after the acute phase with a combination of steroids and intermittent i.v. vincristine. Recently, reports of a beneficial effect of interferon in the treatment of the HES have been published [20, 21].

In conclusion, these two patients illustrate two important notions: first, the cytotoxic potential of the eosinophil, with the possibility of triggering severe lung damage that can lead to the development of ARDS; second, the risk for patients presenting with hypereosinophilia of developing major complications after general anaesthesia. We suggest that perioperative steroid cover may be an important precaution to minimize the risk in any patient presenting with a greatly increased eosinophil count before operation.

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British Journal of Anaesthesia 1992; **69**: 657–658

USE OF SUCTION CATHETERS AS AN ALTERNATIVE TO TRACHEAL TUBES IN ADULTS

P. S. GATAURE, I. P. LATTO AND H. TAYLOR

SUMMARY

A 16-gauge suction catheter (i.d. 4.0 mm) was used to intubate the trachea in two patients in whom the larynx was narrowed as a result of pathological lesions, and normal, small diameter tracheal tubes were too short. (Br. J. Anaesth. 1992; **69**: 657–658)

KEY WORDS

Equipment: suction catheter. Intubation: tracheal.

Narrowing of the airway in adult patients is a relatively uncommon occurrence. When it occurs, it may result in severe difficulties in airway management. We report the use of a suction catheter to intubate the trachea in two such patients.

CASE REPORTS

Patient No. 1

A 15-yr-old girl weighing 50 kg presented for direct laryngoscopy and excision of a laryngeal web. She had previously received multiple surgical and laser treatments for recurrent laryngeal polyps. Her presenting complaints were shortness of breath and inspiratory stridor after walking up a flight of stairs. At indirect laryngoscopy before operation, the ENT surgeons failed to see the larynx. At the patient's previous general anaesthetic 2 years previously, a size 4.0 mm i.d. tracheal tube had been used.

The patient was premedicated with temazepam 20 mg orally 90 min before induction of anaesthesia. After cannulation of a vein, anaesthesia was induced with an increasing percentage of halothane in oxygen. When an adequate depth of anaesthesia had been reached, direct laryngoscopy was performed. This showed that the anterior parts of the vocal cords were fused and the laryngeal inlet was small, approximately 4.0 mm in diameter. There appeared to be no movement of the cords in relation to ventilation, therefore a neuromuscular blocker was not given to facilitate intubation. A size 4.0 mm i.d. tracheal tube was passed through the laryngeal inlet. This was the largest tracheal tube that would pass through the narrowed larynx. However, the distal end of the tracheal tube was only 1.0 cm past the laryngeal inlet, with the proximal end abutting the teeth. It was considered that the tube could be dislodged easily from the trachea as a result of surgical manipulation or neck movement. It was decided, therefore, to intubate the trachea with a 16-gauge suction catheter (4.0 mm i.d.). A 15-mm Portex tracheal tube connector which is normally attached to a size 4.0 mm tracheal tube was attached to the suction catheter. This was connected to a catheter mount. The suction catheter was passed with ease and its position adjusted. The lungs were inflated manually without difficulty and bilateral air entry was confirmed. Neuromuscular block was produced with atracurium 25 mg and intermittent positive pressure ventilation commenced using a Manley MP2 ventilator. A tidal volume of 350 ml with a fresh gas flow of 4.0 litre was delivered to the patient. Anaesthesia was maintained with nitrous oxide and enflurane in oxygen, and fentanyl 50 µg. Tracheotomy was performed and the suction catheter removed. A laryngoplasty was then performed and residual neuromuscular block antagonized with neostigmine 2.5 mg and atropine 1.2 mg. The patient made a good recovery and was discharged from hospital 5 days later.

Patient No. 2

A 65-yr-old man was admitted with severe inspiratory stridor after radiotherapy to a laryngeal tumour. Emergency laryngectomy was planned: he was fasted and no premedication was prescribed.

After cannulation of a vein, anaesthesia was induced with nitrous oxide and an increasing percentage of halothane in oxygen. When the depth of anaesthesia was adequate, direct laryngoscopy was performed. This revealed a large circumferential tumour which obscured most of the laryngeal inlet, except for a small posterior aperture of approximately 4.5 mm in diameter. Attempts to intubate the trachea with a size 4.0 mm tracheal tube failed, as the tube was not long enough to pass into the trachea, therefore a 16-gauge suction catheter (4.0 mm i.d.) was passed into the trachea and a 15-mm Portex tracheal tube connector attached to it. The lungs were inflated manually without difficulty and the correct position of the catheter confirmed by auscultation. Neuromuscular block was produced with atracurium 30 mg and intermittent positive pressure ventilation commenced. Anaesthesia was maintained with nitrous oxide and enflurane in oxygen and fentanyl 75 µg. A minute volume of 4.5 litre was delivered to the patient by a Manley MP2 ventilator

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without difficulty. Tracheotomy was then performed and the suction catheter removed. Laryngectomy was carried out subsequently and the residual neuromuscular block antagonized with neostigmine 2.5 mg and glycopyrronium 0.5 mg. The patient was transferred to the high dependency unit, where he stayed for 24 h. He was discharged from hospital 2 weeks later.

DISCUSSION

As far as we are aware, the use of a suction catheter to intubate the trachea in adults has not been described. Suction catheters have been used to assist blind nasal intubation [1, 2] and to change a nasotracheal tube [3].

Previous experience had led a senior operating department assistant to prepare a trolley with moderately rigid plastic suction catheters (Pennine Healthcare Products) for use in the anaesthetic room of the ENT theatre. An aluminium, plastic-coated stillete was well lubricated to facilitate both insertion and removal from the suction catheter. The stillete was used to obtain the desired curvature of the catheter. In addition to the 16-gauge suction cathether (i.d. 4.0 mm, o.d. 5.0 mm), a 14-gauge catheter (i.d. 3.5 mm, o.d. 4.5 mm) is kept on the trolley. The latter has never been used in our hospital. Both these catheters are 44 cm long and have two marks, 2 cm and 3 cm from the distal end, which allow the anaesthetist to pass the catheter tip to a known distance beyond the cords. For future use, if required, both catheters have been cut to a length of 25 cm to minimize resistance to gas flow. In comparison, a size 4.0 Portex tracheal tube is 21 cm long and a size 5.0 tracheal tube 24.5 cm long. A size 4.0 mm tracheal tube (uncut length of 21 cm) should normally be long enough to intubate the trachea of an adult female. It is possible that the tube used in the first patient had been cut, but this was not checked at the time. Portex manufacture tracheal tubes (Croup tube: Ref. No. 100/112 size of tube) that would have been suitable in both these patients. The Croup tube is available in size ranges 2.5 mm i.d. (22 cm long) to 5.0 mm i.d. (33 cm long). These tracheal tubes are not available in our hospital. A suction catheter proved to be a suitable alternative.

In both of our patients, deep anaesthesia was induced using a mask to enable direct laryngoscopy to be performed. It would have been possible to proceed with the tracheotomy under mask anaesthesia, but we felt there was a risk of losing the airway. In both patients the airway was maintained relatively easily and safely by correct placement of the suction catheters in the trachea. The decision to proceed to laryngectomy after tracheotomy was made before operation by the consultant ENT surgeon.

Cricothyroid puncture and high-frequency jet ventilation were not considered because the cannula might have interfered with the surgery. Intubation either under local or general anaesthesia using an adult fibreoptic bronchoscope would not have been possible, because the smallest tracheal tube that can be passed over the bronchoscope with care is a 6.0-mm i.d. tube. We do not possess a paediatric fibreoptic bronchoscope, and therefore could not have used a smaller tracheal tube. Tracheotomy under local anaesthesia could have been used and would have been necessary had the technique failed.

We recommend that either suction catheters, or a selection of Croup tubes, are available when adults with upper airway obstruction are being anaesthetized.

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British Journal of Anaesthesia 1992; **69**: 659–660

COMMENTARY

GUEST REVIEWERS FOR 1992

Each manuscript submitted to *British Journal of Anaesthesia* is reviewed by members of the Editorial staff, and also by individuals with particular expertise in the area of study under consideration. All reviewers are asked to consider the scientific merit of each communication and its relevance to the clinical practice of anaesthesia. Consequently, acceptance for publication is based on the views of two or more individuals as to originality, validity and clinical relevance of the information presented.

The Editor would like to acknowledge the significant contribution made by the undernoted individuals who, in addition to the Editorial team, reviewed manuscripts during 1992.

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British Journal of Anaesthesia 1992; **69**: 661–665

CORRESPONDENCE

HYPOXAEMIA AND INSERTION OF THE LARYNGEAL MASK AIRWAY

Sir,—In their study on arterial saturation during induction of anaesthesia and insertion of the laryngeal mask airway (LMA), Haynes, Allsop and Gillies [1] have observed a 3% failure rate and 18% rate of difficulty of insertion of the LMA. This has been attributed to inadequate depth of anaesthesia with propofol. As part of an ongoing investigation, we have studied arterial saturation during the insertion of the LMA under neuromuscular block as described by Brain and co-workers [2], in 20 ASA I adult, unpremedicated patients undergoing elective surgery.

Arterial saturation was monitored using a Horizon 1000 pulse oximeter (Mennen Medical) in the 3-s updating mode. Patients' lungs were not preoxygenated. Anaesthesia was induced with i.v. thiopentone 3–5 mg kg^{-1} and 66% nitrous oxide in oxygen administered via a tightly fitting face mask and Bain system at 6 litre min^{-1} from the time of the loss of eyelash reflex. The patients were given suxamethonium 1.5 mg kg^{-1} and the lungs were ventilated manually for 1 min. We had difficulty in insertion of the LMA in one patient and no failures. The average time for securing the airway from the end of manual ventilation was 33.5 (SD 7.73) s. The low rates of difficulty and failure are probably explained by the use of a neuromuscular blocking drug. In cases where the requirements of surgery necessitate controlled ventilation, we feel that insertion of the LMA under neuromuscular block is a viable alternative to insertion under propofol or inhalation anaesthesia.

In our study, the median values of Sp_{O_2} at various times were: preinduction, 98% (range 95–100%); smallest value from cessation of manual ventilation to securing the airway, 98% (93–100%); smallest value in the subsequent 3 min, 99% (96–100%). A decrease in Sp_{O_2} to less than the preinduction value occurred in seven of 20 patients, compared with 19 of 25 in the manual ventilation group of Haynes and colleagues. None of our patients had an Sp_{O_2} less than 90% at any time. This can be attributed to the early and effective administration of manual ventilation for 1 min immediately after suxamethonium. In the light of our observations, we cannot agree with the authors' conclusion that manual ventilation at induction of anaesthesia does not prevent hypoxaemia.

L. N. Yaddanapudi
L. Kashyap
A. Mallick
New Delhi, India

1. Haynes SR, Allsop GW, Gillies GWA. Arterial oxygen saturation during induction of anaesthesia and laryngeal mask insertion: prospective evaluation of four techniques. *British Journal of Anaesthesia* 1992; **68**: 519–522.
2. Brain AIJ, McGhee TD, McAteer EJ, Thomas A, Abu-Saad MAW, Bushman JA. The laryngeal mask airway; development and preliminary trials of a new type of airway. *Anaesthesia* 1985; **40**: 356–361.

Sir,—Thank you for an opportunity to respond to the letter from Drs Yaddanapudi, Kashyap and Mallick. I was most interested to hear of their findings. I would agree that their low incidence of difficulty with insertion of the laryngeal mask airway (LMA) may reflect the improved conditions achieved with neuromuscular block, assuming that they applied a similar criterion for difficulty.

I believe that the likely explanation for the marked differences in results between their study and ours for arterial oxygen saturation values associated with insertion of the LMA after manual ventilation lies in the fact that the two studies have followed different designs. Our patients were premedicated with temazepam, anaesthesia was induced with fentanyl and propofol and the lungs ventilated with five tidal breaths of 100% oxygen before insertion of the LMA. Their patients were unpremedicated, anaesthesia was induced with thiopentone and suxamethonium and the lungs ventilated manually with 33% oxygen for 1 min before LMA insertion.

As we stated in our study, in most instances the decrease in saturation values in the group receiving manual ventilation occurred before effective hand ventilation rather than during subsequent LMA insertion. Clearly, for these patients, using this procedure, effective hand ventilation could not prevent hypoxaemia as it had already occurred. The concluding sentence of our paper, "Manual ventilation at induction of anaesthesia was not effective in preventing hypoxaemia." was intended to be taken in the context of the findings of our study.

G. W. A. Gillies
Glasgow

VOCAL CORD MOVEMENT ON INDUCTION OF ANAESTHESIA

Sir,—In the recent fibreoptic study of movements of the human vocal cords during induction of anaesthesia [1], the authors observed significantly greater decreases in the angle between the cords on induction with thiopentone than with propofol. The decreases were attributed to reflex adduction of the cords and were thought to imply that the tendency to laryngeal spasm was greater with thiopentone.

An antithetical interpretation may possibly be more appropriate. The decreased angle between the vocal cords could have resulted, not from active reflex adduction, but from drug-induced paresis of the intrinsic laryngeal muscles, giving a result similar to that of classical bilateral mechanical injury to the recurrent laryngeal nerves, namely, narrowing of the glottis.

Because of the oblique axis of the cricoid facet of the cricoarytenoid joint [2], when the tonic postural activity in the cricoarytenoid muscles is impaired, the arytenoid droops passively so that the vocal process points downward and medially towards its fellow of the opposite side. There is then a tell-tale convergence of the vocal processes as viewed from above, whereas with active adduction the arytenoids do not sag and the vocal processes point almost directly forward.

If the reported narrowing of the rima glottidis with induction happened to be of the passive variety, it would imply that thiopentone diminished the activity of the laryngeal muscles more than did propofol, which is of course the reverse of what the authors inferred. It would be interesting to know if their videotape pictures show the direction of the vocal processes clearly enough to decide which is the correct interpretation.

B. R. Fink
Seattle

1. Barker P, Langton JA, Wilson IG, Smith G. Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol. *British Journal of Anaesthesia* 1992; **69**: 23–25.
2. Sonesson B. Die funktionelle Anatomie des Cricoarytaenoidgelenkes. *Zeitschrift für Anatomie und Entwicklungsgeschichte* 1959; **121**: 292–303.

Sir,—Dr Fink's hypothesis is that thiopentone may cause a greater reduction in the activity of the intrinsic laryngeal muscles than propofol, producing drug-induced paresis of these muscles. In the design of our study, we did not attempt to measure the activity of the intrinsic laryngeal muscles and therefore we cannot draw any conclusions relating to this point.

However, if thiopentone produced paresis of the intrinsic muscles, then we should have expected the vocal cords to have assumed the cadaveric position, similar to that seen after administration of neuromuscular blocking drugs. In fact, we observed that in some patients, who received thiopentone, the vocal cords closed completely.

In a recent study by Drummond [1], the influence of thiopentone on upper airway muscles was investigated. He concluded that, after the use of thiopentone for induction of anaesthesia, there was a change in the *pattern* of activity of the upper airway muscles, rather than a reduction in the magnitude of their activation.

Our paper referred to overall reflex activity in the upper airway after induction of anaesthesia with either thiopentone or propofol. Common clinical experience suggests that, after thiopentone, reflex activity in the upper airway is greater than after propofol, but the mechanism for this effect is unknown.

We have reviewed our video recordings as suggested by Dr Fink, but unfortunately it is not possible to demonstrate with any degree of certainty the direction of movement of the vocal processes.

J. Langton
I. Wilson
P. Barker
G. Smith
Leicester

1. Drummond GB. Influence of thiopentone on upper airway muscles. *British Journal of Anaesthesia* 1989; **63**: 12–21.

SPINAL ANAESTHESIA FOR CAESAREAN SECTION

Sir,—The paper by Vucevic and Russell [1] on spinal anaesthesia for Caesarean section raises several interesting considerations.

First, one patient in the study had a dural tap with the extradural catheter. Accidental insertion of the extradural catheter into the subarachnoid space through the dural hole made by the spinal needle has always been quoted as one of the potential dangers of using the needle-through-needle technique. However, until now, there has been no report in the world literature of this happening since the advent of the technique.

Second, it is not clear what criteria, if any, the authors used to determine which patients required an extradural top-up. For example, close analysis of tables III and IV shows that patient No. 10 had a top-up 2 min after being turned to the supine position. The levels of sensory analgesia and anaesthesia as assessed by the authors at this time were T4 and T7, respectively. However, patient No. 31 did not receive a top-up until 30 min after being turned to the supine position. The levels of sensory analgesia and anaesthesia in this patient after 2 min in the supine position were T9 and T10, respectively, and remained so for a further 10 min. Does this imply that surgery was commenced before T4 analgesia was achieved?

Third, do the authors feel that we should be using larger volumes of more dilute solutions of bupivacaine when providing subarachnoid anaesthesia for Caesarean section rather than 3.0 ml of 0.5% plain bupivacaine, and if so what volume and concentration do they recommend? However, we feel that 12 ml of 0.125% bupivacaine may be a slightly excessive volume to use, especially if the patients are turned supine immediately after the subarachnoid injection. The median value for sensory anaesthesia (12-ml group) after 5 min in the supine position was T2. However, these patients had spent 30 min in the right lateral position and if they had been turned supine immediately after the subarachnoid injection, a larger volume of unbound drug would have been available to travel rostrally in the cerebrospinal fluid, and the maximum height of sensory anaesthesia achieved would have been much higher.

M. Patel
A. Swami
London

1. Vucevic M, Russell IF. Spinal anaesthesia for Caesarean section: 0.125% plain bupivacaine 12 ml compared with 0.5% plain bupivacaine 3 ml. *British Journal of Anaesthesia* 1992; **68**: 590–595.

Sir,—Accidental insertion of an extradural catheter through the hole made in the dura by a spinal needle is, indeed, a theoretical risk of a needle-through-needle technique. The details of this patient were submitted as a case report to a peer review journal, but the report was rejected on the grounds of "faulty technique" because the "dural puncture could have been caused by the Tuohy needle" and "the grounds for believing the catheter passed through the hole made by the spinal needle are rather tenuous". In our investigation, to reduce the risk of spinal headache and minimize damage to the tip of the spinal needle, both needles were inserted with their bevels facing laterally (but in opposite directions). Before the catheter was threaded, the extradural needle was rotated 90° to face cephalad. This rotation is believed to increase the risk of accidental dural puncture.

The main criterion used to decide on a top-up was a failure of the spinal to spread adequately. Drs Patel and Swami are to be congratulated for drawing our attention to patient No. 31: there is an error in the data and this patient received her extradural top-up at 10 min. One could argue about the exact definition of adequate spread, but after many years of experience we have found that, if low levels of block do not show signs of significant extension after turning the patient from the lateral to supine position, then anaesthesia is inadequate. While it could be argued that we were rather quick to top up the extradural in patients Nos 6, 7, 9 and 10, the lack of spread in patients Nos 11 and 31 support this approach.

Our knowledge of the clinically relevant factors governing the spread of spinal anaesthesia is incomplete and we cannot suggest a suitable volume or concentration of plain bupivacaine. However, Van Zundert and colleagues [1] injected 10 ml of 0.125% bupivacaine (with adrenaline) as a bolus and then turned their patient. They commented that levels of block were similar to those produced with 3 ml of 0.5% plain bupivacaine.

The principal point of this study, and its predecessor in which up to 18 ml of 0.08% bupivacaine was used [2], is to indicate that the spread of spinal anaesthesia involves some poorly understood and complex hydrodynamic interactions between several fluid compartments.

I. F. Russell
M. Vucevic
Hull

1. Van Zundert AA, Wolf AM, Vaes L, Soetens M. High volume spinal anesthesia with bupivacaine 0.125% for Cesarean section. *Anesthesiology* 1988; **69**: 998–1003.
2. Russell IF. Cesarean section and spinal anesthesia with dilute solutions of bupivacaine: The relationship between infused volume and spread. *Regional Anesthesia* 1991; **16**: 130–136.

METALLIC FRAGMENTS AND THE COMBINED SPINAL–EXTRADURAL TECHNIQUE

Sir,—Some anxiety may have been caused recently by suggestions in this journal [1, 2] and elsewhere [3] that, during the needle-through-needle method of combined spinal–extradural anaesthesia, the spinal needle tip may be damaged by contact against the inner aspect of the extradural needle, and even that metallic fragments might be produced. These allegations may be worrying particularly to those anaesthetists without access to facilities to confirm or refute them, and their implications are serious enough to merit further theoretical consideration and experimental investigation.

When a cutting-tipped spinal needle and a Tuohy needle are used together, there are three possible relative alignments of the bevels: parallel to, facing or at 90° to each other. I have studied these combinations under the microscope, and only when the bevels are parallel does the spinal needle tip make contact with the inner surface of the extradural needle. During the needle-through-needle technique, when the spinal needle is being inserted, the Tuohy needle bevel should be facing cephalad. As normal spinal technique requires the needle to be inserted through the dura with its bevel laterally, the relative alignment of the two needles is at right-angles—one of the "safe" alignments. Surprisingly, there is no reference to the relative position of the needle bevels in the most critical letter [3].

There are other theoretical considerations. Different gauges of spinal needle pass with varying ease through different gauges of extradural needle, and gauge size allows the manufacturers some variation in the external diameter of spinal needles and internal diameter of extradural needles. The latter also depends on the thickness of the needle wall, which varies between different makes. The needle combination chosen by Eldor and Brodsky [3] (a 25-gauge Braun spinal needle through an 18-gauge Portex extradural needle) was particularly unfortunate as it produces an unusually "tight fit". However, even with this combination, contact by the spinal needle tip does not occur when the bevels are aligned at 90° to each other. Another factor is the radius of bend of the tip of the Tuohy needle, a smaller radius making contact by the spinal needle tip more likely.

The final theoretical consideration involves pencil-point spinal needles. Only the shoulder of a pencil-point tip makes contact with the inside of the Tuohy needle curve so that, in addition to their other advantages, these needles theoretically are preferable for needle-through-needle techniques.

Both Portex U.K. Ltd, using an indepedent institute for biomedical equipment evaluation to test a variety of spinal and extradural needle combinations, and the Becton Dickinson company, using their own technical department to test their own spinal–extradural needle sets, have investigated the possibility of spinal or extradural needle damage and the production of metallic particles. In addition to microscopic examination, tests included energy-dispersive x-ray analysis of any particulate matter found. In none of the tests was any damage found to the tip of the spinal needle. Some extradural needles showed fine markings after the test, as reported by Eldor and Brodsky [3], but such marks were also present before the tests and are part of the normal manufacturing process. Neither investigation found any evidence of metallic particulate contamination.

In summary, while there is no evidence of spinal or extradural needle damage during needle-through-needle combined spinal–extradural anaesthesia, it is preferable to use pencil-point needles or very fine spinal needles and an extradural needle having a tip with a generous radius of curve. It is also wise to use one of the manufacturers' needle combinations recommended specifically for the technique. Examples include those from Portex, which combine 26-gauge cutting or pencil-point spinal needles with 16- or 18-gauge extradural needles, from Becton Dickinson, who provide a choice of 25- or 27-gauge cutting or pencil-point spinal needles and Braun, whose new Espocan system contains a spinal needle with a plastic sleeve which holds it centrally in the extradural needle lumen and guides it through a hole cut in the outer curve of the extradural needle tip.

L. E. S. Carrie
Oxford

1. Brownridge P. Spinal anaesthesia in obstetrics. *British Journal of Anaesthesia* 1991; **67**: 663.
2. Eldor J. Combined spinal–extradural anaesthesia in obstetrics. *British Journal of Anesthesia* 1992; **68**: 634.
3. Eldor J, Brodsky V. Danger of metallic particles in the spinal–epidural spaces using the needle-through-needle approach. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 461.

Sir,—In previous correspondence, Dr Carrie has written that "The origin of many innovations seems to lead back inevitably to Biblical times" [1]. So I searched there and found that "Iron sharpeneth iron; so a man sharpeneth the countenance of his friend" [2]. It is not necessary to be a metallurgist to understand that, when metal passes through another bent metal, it causes friction. Friction causes metallic fragments. The question is not if there are metallic particles, but if they have any clinical significance, or if there is a way to avoid them. Concerning the first question—it is too early to judge. We need to investigate the impact of these small particles on the spinal cord to determine both early and late implications. As to the second question—we can straighten the extradural needle tip, but create a problem in introducing the catheter. Alternatively, the Eldor needle consists of an 18-gauge extradural needle with a 20-gauge external spinal conduit. The spinal needle is introduced through the straight guide tube with no bent tip, so avoiding the problem.

I encountered this problem with my previous needle [3] and have abandoned it. To my surprise, companies (Portex, Becton Dickinson, Braun, etc.) continue to market these packs, even after my observations [4].

Dr Carrie uses the word "contact" throughout his letter. I think it should be replaced by "friction", as it is obvious that contact between the two needles cannot be avoided. I have found no difference between any alignment, or any spinal needle, including a pencil-point tip needle.

I have not seen the results of the work by Portex or Becton Dickinson, although I also was told by Portex that "Independent laboratory tests conducted by Portex show no metal particles produced on passing 26-gauge spinal needles through 16-gauge and 18-gauge Tuohy needles" [Russell CA, personal communication].

Dr Carrie said that "some extradural needles showed fine markings after the test". With enough magnification these "fine" markings would become "not fine". I cannot understand the next sentence that "such marks were also present before the tests". This kind of remark arouses much suspicion. Sir Arthur Conan Doyle wrote: "How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth".

J. Eldor
Jerusalem

1. Carrie LES. First use of combined spinal–extradural anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 667.
2. *Proverbs* 27: 17.
3. Eldor J, Chaimsky G. Combined spinal–epidural needle (CSEN). *Canadian Anaesthetic Society Journal* 1988; **35**: 537–538.
4. Eldor J, Brodsky V. Danger of metallic particles in the spinal–epidural spaces using the needle-through-needle approach. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 461.

INSPIRATORY TO END-TIDAL OXYGEN DIFFERENCE

Sir,—I wish to comment on the interesting article by Bengtson and colleagues [1] on oxygen difference monitoring.

In my experience (I use oxygen and nitrous oxide with isoflurane in a low-flow system, ventilating manually to maintain an end-tidal carbon dioxide concentration of ±4.5 vol%) the *rate* of ventilation influences $(\mathrm{I}_{\mathrm{O_2}}-\mathrm{E}'_{\mathrm{O_2}})$ inversely, complicating the interpretation of the oxygen difference further. $(\mathrm{I}_{\mathrm{O_2}}-\mathrm{E}'_{\mathrm{O_2}})$ is merely a tidal measurement; to judge oxygen uptake the dimension "time" must be considered. To maintain $\mathrm{E}'_{\mathrm{CO_2}} = 4.5$ vol% I can, for example, ventilate 14 times per minute with a tidal volume of 470 ml, or 8 times 730 ml ... this causes an increase in $(\mathrm{I}_{\mathrm{O_2}}-\mathrm{E}'_{\mathrm{O_2}})$; meantime the $Sa_{\mathrm{O_2}}$ will be constant at ±98% and I assume that the oxygen uptake will also be constant. Is this assumption incorrect?

M. Schrader
Witten-Buchholz, Germany

1. Bengtson JP, Haraldsson Å, Bengtsson A, Henriksson B-Å, Stenqvist O. Inspiratory to end-tidal oxygen difference during nitrous oxide anaesthesia. *British Journal of Anaesthesia* 1992; **68**: 599–602.

Sir,—We thank Dr Schrader for his comment. An increase in $(\mathrm{I}_{\mathrm{O_2}}-\mathrm{E}'_{\mathrm{O_2}})$ is seen as a result of acute hypoventilation, decreased uptake of nitrous oxide, increased inspired oxygen concentration and increased oxygen uptake rate.

Dr Schrader has experience of an increase in $(\mathrm{I}_{\mathrm{O_2}}-\mathrm{E}'_{\mathrm{O_2}})$ as a result of a decreased ventilatory frequency with a constant minute ventilation volume. As far as we understand, this is best explained by a change in $V\mathrm{D}/V\mathrm{T}$ such that alveolar ventilation has decreased. If this is true, the end-tidal carbon dioxide concentration will also subsequently increase.

J. P. Bengtson
Å. Haraldsson
A. Bengtsson
B.-Å. Henriksson
O. Stenqvist
Göteborg, Sweden

PRE-EMPTIVE EXTRADURAL ANALGESIA

Sir,—We congratulate Dr Dahl and co-authors [1] on their interesting and fundamental study on pre-emptive extradural analgesia in the context of major abdominal surgery. This topic is most important for both surgeons and anaesthetists, and we feel that it is paramount to try to understand why this study apparently failed to produce the results to be expected from previous experimental work [2].

We wish to raise the following points:

Why was the combination of extradural bupivacaine and morphine chosen? Morphine has not only slow and unfavourable kinetics, particularly when used extradurally [3], it may also—under certain circumstances—possess excitatory [4, 5] and anti-analgesic properties (either directly [6, 7] or via its 3-glucuronide metabolite, particularly when given spinally [8]). Spinal morphine has been shown not to decrease MAC [9], whereas spinal fentanyl does reduce MAC [10]. Bupivacaine has not been proven to have the same specific antinociceptive and anti-wind-up potential as lignocaine [11, 12] when applied locally or systemically. In the extradural doses used, significant (and pharmacologically effective) plasma concentrations of local anaesthetic result. A systemic antinociceptive action of bupivacaine (which lignocaine possesses [13]) has not been demonstrated so far. Thus it would appear that the combination bupivacaine–morphine is antinociceptively less favourable than, for example, lignocaine–fentanyl. These factors, together with the conservative extradural dosage regimens used in the study, would further support the authors' conclusion that, in fact, afferent block was insufficient to produce "true" (or complete) pre-emptive analgesia.

It seems possible that the study did, in fact, show some effect. Demonstrating pre-emptive analgesia is probably easiest via its effects on cumulative analgesic consumption in the first 24 h after operation. Although the *number* of patients receiving additional morphine in this period was the same in both groups, the *amount* of morphine given to achieve similar visual analogue pain scores (VAPS) was not (50 mg *vs* 170 mg, in favour of the pre-emptive group). This difference is particularly convincing because it results from analgesia given on patient demand by nursing staff—a measure of postoperative analgesia known to be less sensitive than that achieved when using patient controlled analgesia pumps [14].

It is not clear if postoperative VAPS or analgesic requirements represent adequate end-points for studying the effects of pre-emptive analgesia. From experimental considerations [2, 15], it would appear that hyperalgesia (increased sensitivity and extended sensory fields) is the earliest and most sensitive manifestation of inadequate antinociceptive control. This could perhaps be investigated by measuring sensory and pain cutaneous thresholds [16].

In conclusion, we feel that this study should not be considered as disproving the concept of pre-emptive analgesia, but rather as providing an interesting insight into the questions and problems which remain to be solved before this concept can be realized in clinical practice.

O. H. G. Wilder-Smith
A. Borgeat
M. Tramèr
D. R. Morel
Geneva

1. Dahl JB, Hansen BL, Hjortsø NC, Erichsen CJ, Møiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *British Journal of Anaesthesia* 1992; **69**: 4–8.
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3. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. *Anesthesiology* 1984; **61**: 276–310.
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6. Huang LYM. The excitatory effect of opioids. *Neurochemistry International* 1992; **20**: 463–468.
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12. Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* 1992; **48**: 261–268.
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15. Dubner R. Hyperalgesia and expanded receptive fields. *Pain* 1992; **48**: 3–4.
16. Wilder-Smith OHG, Borgeat A, Hoffmann A-C, Rifat K. Fentanyl or magnesium analgesic supplementation of anesthesia: effect on post-operative sensory thresholds. *Anesthesiology* 1992; **76** (Suppl.): (in press).

Sir,—We appreciate the comments made by Dr Wilder-Smith and colleagues on our paper on pre-emptive extradural analgesia in major abdominal surgery. They propose that bupivacaine and morphine may not be the optimal combination of analgesics, that the amount of additional morphine was in favour of the pre-emptive group, and finally that postoperative pain may not represent adequate end-points in the study of pre-emptive analgesia.

In our study, we used bupivacaine and morphine because, in *clinical* trials, the effect of this combination for postoperative analgesia is well documented compared with other regimens (see references cited in [1]). However, the *optimal* extradural opioid and local anaesthetic, alone or in combination, for surgical anaesthesia and postoperative analgesia is unknown and, so far, a total afferent block during and after operation has not been documented by any regimen during major abdominal surgery. The *clinical* implications of the specific antinociceptive and anti-wind-up potential of local or systemic lignocaine observed in experimental studies, and the potential value of systemic lignocaine in the treatment of postoperative pain, have not yet been settled. In a recent study, however, no significant differences in morphine requirements or pain scores could be demonstrated between patients with an inguinal field block with lignocaine performed before, compared with after surgery [2].

The *amount* of additional morphine 0–24 h after operation was not statistically different between groups and represents only three and four patients. No statistical difference in morphine requirements, and no trend, was observed 24–72 h after operation.

In our opinion, pain scores and analgesic requirements represent adequate end-points for studying the effects of clinical pre-emptive analgesia. However, additional assessment of pain and sensory thresholds is interesting, and deserves further evaluation [3].

In conclusion, our regimen may not have provided total afferent nociceptive block during surgery. Thus further studies are needed to compare the effects of different neural block to clarify the clinical significance of pre-emptive analgesia in postoperative pain. Finally, we emphasize that afferent nociceptive stimuli may not only sensitize dorsal horn neurones *during*, but also *after* tissue injury, and that factors other than timing of the analgesic treatment may be important to reduce post-injury CNS-hyperexcitability [4, and in preparation].

J. B. Dahl
B. L. Hansen
N.-C. Hjortsø
C. J. Erichsen
S. Møiniche
H. Kehlet
Hvidovre, Copenhagen

1. Dahl JB, Rosenberg J, Hansen BL, Hjortsø N-C, Kehlet H. Differential analgesic effects of low-dose epidural morphine and morphine–bupivacaine at rest and during mobilisation following major abdominal surgery. *Anesthesia and Analgesia* 1992; **74**: 358–361.

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SKIN INJURY WITH A PULSE OXIMETER

Sir,—We were interested in the report of skin injury in an infant with pulse oximetry [1], but doubt if this was a thermal injury or caused by a phototoxic reaction. We recently observed a lesion on the pulp of a patient's finger after removal of a Datascope Flexisensor which had been in place overnight. The lesion was similar to that described in the case report, being bullous and approximately 5 × 5 mm in extent. Examination of the relative position of the lesion and the diodes of the pulse oximeter suggested that thermal injury was most unlikely and that pressure from a fold that consistently develops on the inner surface of the Datascope Flexisensor was a more likely cause. This was confirmed in subsequent patients in whom a distinct pressure groove could be seen in relation to the fold in the Flexisensor immediately after its removal.

In addition, we are unable to understand the methodology used by Pettersen, Kongsgaard and Aune to find a maximum temperature of 23.6 °C under a sensor probe during use. Using thermocouples between the diodes and the subject's finger, we found that the temperature under the Datascope Flexisensor probe was related to the temperature of the subject's skin. Thermocouples between the diodes and the finger registered a temperature up to 6 °C greater than the skin temperature of the adjacent finger, resulting in maximum temperatures of 40–42 °C in normal, well-perfused anaesthetized patients.

Following our initial observations, instructions were issued to ensure that the probes were not wrapped tightly around the end of the finger, there has been no recurrence of this type of injury and examination of patients' fingers immediately after removal of Flexisensors have failed to show the pressure grooves noted before. The solution adopted in the case report could have had a similar effect, as pressure from irregularities following folding of the probe may have been dissipated against the toe nail. Alternatively, following observation of a problem, the sensor may have been placed with more care, avoiding tight folding around the end of the toe.

While the case report referred to the Datex Flexalite probe, the causation of the injury may be related to flexible sensors in general and be similar to the problem we have observed with the Datascope Flexisensor.

D. W. Bethune
N. Baliga
Cambridge

1. Pettersen B, Kongsgaard U, Aune H. Skin injury in an infant with pulse oximetry. *British Journal of Anaesthesia* 1992; **69**: 204–205.

Sir,—We appreciate the questions and comments made by Drs Bethune and Baliga regarding our report. Thermal injury was discussed among various other possible causes. Drs Bethune and Baliga have observed a similar lesion and suggest pressure from a fold developing on the inner surface of the sensor to have caused the harm. A similar mechanism in our patient cannot be ruled out, although none of our other patients has presented such lesions.

The skin temperature under the sensor was determined by placing a small temperature probe underneath the diode, attached to the patient's finger. Under these conditions, the skin temperature never increased beyond 33.6 °C in the reported patient, not 23.6 °C which appeared erroneously in our report. We have now made a small study measuring pulp temperature on the 5th finger before and during pulse oximetry in five female volunteers. A tiny sensor (West Temperature Probe 2070 with Copper Constantan sensor tip, 0.14 mm^2) was placed underneath the diode without blocking the light emission. Mean pulp temperature before pulse oximetry was 31.4 °C (range 27–34 °C) and mean temperature during ongoing pulse oximetry was 32.0 °C (range 28–34 °C). Mean temperature increase during pulse oximetry was 0.6 °C (range 0–1 °C).

Obviously, modern pulse oximetry devices should not be relied upon completely from a safety point of view. A high level of alertness is always appropriate when patients are connected to technical devices.

B. Pettersen
U. Kongsgaard
H. Aune
Oslo

British Journal of Anaesthesia 1992; **69**: 666–668

BOOK REVIEWS

Respiratory Monitoring (*Contemporary Management in Critical Care* series). Edited by M. J. Tobin. Published (1991) by Churchill Livingstone, Edinburgh, London, Melbourne, New York, Tokyo. Pp. 258; indexed; illustrated. Price £22.50.

This is largely a North American view of respiratory monitoring, with frequent reminders of the distinctions between the American and English languages: "data" are almost invariably singular, strings of nouns are used as adjectives, and a string of adverbs has been used to split an infinitive real good ("to quickly, non-invasively and accurately measure patient temperature"). I was struck by the contrast between the glimpses of American respiratory ICU management and my recollections of its counterpart in the U.K., and by the explicit and implicit doubts over whether American practice ought to have proceeded down certain avenues, down which British practice has largely declined to follow.

The opening chapter is on the information content of intermittent blood-gas analysis, because this is the gold standard for the technologies of true continuous monitoring of respiratory gas exchange. It is a disappointing compilation of established clinical maxims linked by some curious inversions of their orthodox underlying logic. There are excellent chapters about continuous on-line blood-gas monitoring (including fluorescence fibreoptic methods), transcutaneous and transconjunctival oxygen monitoring, pulse oximetry, capnography and transcutaneous carbon dioxide monitoring. The authors did well here with their circumscribed task of describing the technological developments, their present place and limitations in clinical practice, and the possibilities for the future. The chapter on measurement of mixed venous oxyhaemoglobin saturation lacked scientific rigour: "venous O_2 *levels*" "*fall below 0.68*" (units unspecified); oxygen delivery is abbreviated interchangeably by DO_2 or O_2D; the algebraical statement of the relationships between mixed venous oxyhaemoglobin saturation and the consumption and delivery of oxygen added nothing and contained a minor inaccuracy and a major misprint. The many anecdotes on the usefulness of Sv_{O_2} monitoring were not put together into a convincing overall justification, despite a laboured attempt.

The chapter on respiratory neuromuscular function is an informative account of a subject that tends to be neglected in Britain. Similarly, the chapter on respiratory mechanics is soundly based on the (traditionally difficult) classical algebra, but British clinicians might well ask if some of the measurements (particularly of the work of breathing in patients undergoing ventilation and "auto-PEEP") are made because of *need* or merely *availability*. I suspect (from later reading) that it may reflect the relative popularity of various weaning-assist modes and inverse-ratio ventilatory support in American respiratory care, and an American preference for weaning "scientifically" rather than by educated guesswork.

The last three chapters are aimed at the difficulties looming over information overload. They are the most difficult to read and were probably also the most difficult to write, because they deal, not just with the technology of monitoring, but with the art. I suspect that the penultimate two chapters on computerization, quality control and computer-assisted monitoring and decision-making may reflect what occurs in a leading hospital in this field. However, I wonder at the standard of training of those whose decisions need the support illustrated by the computerized algorithms, although I applaud their likely effects on standardization of treatment, and envy the immediate and complete availability of a patient's information in addition to reminders and alerts from a net-worked bank of expert knowledge.

The last chapter, on cost-effectiveness, struck me as having rather arbitrary terms of reference that substituted accuracy for effectiveness and dealt rather sparingly with cost and hardly at all with the balance between cost and effectiveness. As a devotee of Respiratory Inductance Plethysmography as an academic pursuit, I was delighted but surprised to see it so far up the ratings of cost-effective technologies. This may again reflect an American dream of having something more measurable than common sense behind decisions to ventilate the lungs or wean patients from ventilators. The last sentence of the last chapter is, however, a commendable summary of the book's whole philosophy:

"Indeed, the most pertinent challenge to health care providers is how to monitor wisely."

A. M. S. Black

Principles of Measurement and Monitoring in Anaesthesia and Intensive Care, 3rd Edn. By M. K. Sykes, M. D. Vickers, C. J. Hull, P. J. Winterburn and B. J. Shepstone. Published by Blackwell Scientific Publications, Oxford. Pp. 372; indexed; illustrated. Price £45.00.

This is the third edition of a well known textbook which differs from the previous edition in two very significant ways: the section on statistics has been removed and a new section on the principles of monitoring in clinical practice has been introduced. The other two large subdivisions of the book on the physical basis of measurement systems and the methods of making specific measurements remain, similar in form, but extensively updated. The text is well written, the diagrams are clear and well selected, and the layout is attractive and easy on the eye.

The basic educational objectives of the first part of the book are that the observer should understand upon what principles a measurement is based, and know what other factors might affect its accuracy or generate artefact. It succeeds well in achieving these ends across the whole range of measurements made in anaesthesia and intensive care. It is especially good at identifying just what information can be obtained from a particular measurement and emphasizes the dangers of using derived data. In the main, the text has been improved from the second edition, with a good selection of up-to-date references which will lead the reader on to more specific sources as required. One area that was, however, rather deficient was the chapter on Recorders and Data Storage Devices. Considering that digital data storage and retrieval are so important for the future (especially with automatic data recording and the possibilities of knowledge-based programming), it was disappointing to see the text only minimally updated from the second edition and the same two references present at the end of the chapter, the most recent of which was 12 years old.

The second part of the book, on Specific Measurements, is very good and treats the content much more clearly and rigorously than the majority of other texts. The coverage is comprehensive and the references are well selected and, in the most part, up-to-date. This section also includes measurements which are research tools (e.g. total body plethysmography, xenon clearance), in addition to those which have relevance to clinical monitoring.

The third part of the book deals with the application of the principles and techniques described earlier to the clinical practice of monitoring the major body systems. Rather than concentrate on the practical details and clinical complications of monitoring techniques, the authors have focused on the principles involved in providing a monitoring system which will give adequate warning of a deterioration in the patient's condition or in apparatus malfunction. Here again, the thrust of the text is directed to sound understanding rather than how to overcome practical, day-to-day difficulties and the differing needs of the theatre and ITU environments. There is also rather little discussion of what has come to be termed essential, minimal or adequate monitoring.

In conclusion, this is a good book which succeeds well in its main objective of describing the fundamental and applied principles involved in measurement and monitoring. As such, it deserves to be available in all hospitals which have trainee anaesthetists. Readers will, however, have to consult other texts to obtain advice on practical technique and the avoidance of everyday difficulties, neither of which, in fairness, was intended to be covered by the authors.

P. Hutton

Anaesthesia for Ophthalmic and Otolaryngologic Surgery. Edited by K. E. McGoldrick. Published by W. B. Saunders Company, Philadelphia. Pp. 318; indexed; illustrated. Price £30.50.

This book contains 22 chapters, the majority of which have been written by the editor herself, some in association with co-authors. There are 12 chapters devoted to otolaryngology, including one on trauma, one on difficult intubations and one on paediatric airway emergencies. Nine chapters are devoted to ophthalmology and one to postoperative recovery. There have been two books on anaesthesia related to eye, ear, nose and throat surgery in the past 10–12 years; the last one was published in 1985, so this is a timely addition on the subject.

The editor states that this is a reference book rather than a primer and it contains information on applied physiology, pharmacology and anatomy related to clinical practice. These aims have been fulfilled to a certain extent. On the whole, the sections relating to anaesthesia for ear, nose and throat procedures are dealt with relatively better than the sections relating to anaesthesia for ophthalmic procedures.

There are good chapters on description of paediatric airway emergencies, plans of anaesthesia for bronchoscopy, anaesthesia for thyroid surgery and the larynx. In general terms, the details of anatomy, regional anaesthesia for ENT surgery, description of anaesthesia for laser surgery and its complications and congenital syndromes are well described.

The chapters relating to ophthalmology, however, are relatively scant. The physiology and pharmacology of intraocular pressure (IOP) are rather superficially described; propofol does not even merit a mention regarding its effects on IOP; there is only one sentence relating to it in the whole book. The use of propofol is not mentioned in day-case anaesthesia. Recent literature on the effects of i.v. agents, muscle relaxants and volatile agents in this respect have also been ignored. A "recent" study, showing lack of substantial effect of ketamine on IOP, dates to 1976. The management of the open eye injury is described in the chapter dealing with intraocular pressure and repeated in the following chapter. There is a poor description of peribulbar block using six separate injections and pressure on the globe for 1 min.

There are other aspects of the book which deserve comment. A block monitor is described as unreliable at one place, but a peripheral nerve stimulator is described as important elsewhere. Mallampati's classification of difficult intubations is illustrated by a photograph of a small child. Other classifications described even more recently in the British literature are not mentioned. The laryngeal mask airway is also not mentioned. Some statements may have to be interpreted with caution, such as the author's advice to use ketamine with great caution in patients having maxillofacial surgery when trying to avoid tracheal intubation; sending a patient even with a suspected diagnosis of acute epiglottitis to the x-ray department and subjecting premature infants to surgery on a day basis.

The layout of the book does not appear to follow a logical sequence, resulting in repetition of several subjects, such as tympanostomy (three times in three separate chapters), description of local anaesthesia of the larynx, anaesthesia for tracheotomy, non-cardiogenic pulmonary oedema, anaesthesia for bronchoscopy and postoperative complications of ENT surgery, etc.

The book is well produced; there are very few spelling and typographical mistakes and it is relatively inexpensive. However, although it is described as a reference book, most of the references are fairly old.

J. Gaston and R. K. Mirakhur

Kinetics of Anaesthetic Drugs in Clinical Anaesthesiology. Edited by P. F. White. Published by Baillière Tindall, London. Pp. 316; indexed; illustrated. Price £27.50.

A total of 19 authors have provided contributions for this issue of the *Baillière's Clinical Anaesthesiology* series. The test of a book is the extent to which it is referred to to answer questions or clarify points. The book succeeds in this respect and should prove a valuable reference source. The first chapter is written by the editor and gives an overview of the main groups of drugs available and introduces newer concepts of drug delivery. Broad pharmacokinetic and dynamic principles are explained in the next chapter, which is followed by a detailed description of the pharmacokinetics of i.v. anaesthetics. An overview is provided of the pharmacokinetics of inhaled anaesthetics and the two new inhalation agents which should soon become available are compared with the present agents. Further chapters consider the pharmacokinetics and dynamics of neuromuscular relaxants, opioids, benzodiazepines and the drugs used for their antagonism.

The chapter dealing with vasoactive drugs is particularly comprehensive and includes information on the newer agents such as enoximone. The description of the clinical approach to the use of vasoactive drugs provides sensible guidelines for the selection of the appropriate agent in different clinical situations.

The factors underlying delivery of i.v. anaesthetic drugs and a review of the latest types of infusion systems, including target-controlled, are included in the chapter on the pharmacokinetic basis of i.v. drug delivery. Perhaps inevitably, in the final chapter concerning future directions in drug delivery, there is a degree of reiteration of topics covered previously. However, the principles of transdermal administration are presented, together with a short review of the drugs which are available and those under investigation.

There are several typesetting errors which have passed the proof readers, the most serious of which is a line which has been omitted on p. 637 in the chapter describing the pharmacokinetics of local anaesthetics.

Overall, this monograph on the relevance of pharmacokinetic principles to the use of drugs in anaesthesia succeeds in its aim of providing a valuable and comprehensive source of information for the practising anaesthetist.

G. N. C. Kenny

MCQ Companion to the Textbook of Anaesthesia. By D. Fell, D. R. Derbyshire, A. R. Aitkenhead and G. Smith. Published by Churchill Livingstone, London. Pp. 276. Price £12.50.

Multiple Choice Questions (MCQ) are now a well-established part of the staple diet of examinations for anaesthetists. Devising really good unambiguous MCQ is a difficult task. A sensible way to approach the problem, and the one used here, is to take a standard anaesthetic textbook and compose MCQ from it. The authors are aiming at the level of the F.R.C.Anaes. Part 1 (D.A. U.K.) examination. In fact, the authors have done better for, in addition, they have referenced a standard medical textbook and the National Formulary where necessary, as this examination requires knowledge of general medicine, pharmacology and therapeutics in addition to anaesthesia.

There are four main sections, on Physiology, Pharmacology, Medicine and Anaesthesia, each with 100 MCQ. The layout is pleasing, with the familiar question stem with five true or false options printed on each left-hand page and the matching answers with explanations on the opposite page. This makes it tempting to cheat, so a certain amount of self-discipline is required. The last two sections of the book comprise two mock examinations, each with 60 questions comprising the type of mix of topics that would be encountered in the real examination. Again, the same format is followed of questions on one side of the page, with the answers plus explanations on the opposite page. Unfortunately, the time allowed for these "examinations" is not stated, so the candidate cannot pace himself.

This is a useful book which would be of value to anyone taking any anaesthetic examination in which MCQ are used, such as the Diploma of the European Academy of Anaesthesiology or the Diploma of Anaesthetics (Part 1) of the Royal College of Anaesthetists. It is not intended to cater for those attempting the Part 3 F.R.C.Anaes. examination. The approach is fairly didactic in parts—no doubt necessarily, as the intent is to test the knowledge of students who have practised anaesthesia for up to 2 years. In common with similar books, it suffers on occasions from indecision where undesirable words such as *may*, *mostly*, *probably* or *normally* are used in the question stem, or even the ever-hopeful and desperate "*the following are true*" approach; this should be avoided. Another weakness is the difficulty the authors obviously had on occasions in devising the fifth response to the stem. There are, of course, the odd "catch" questions, but these are of no harm, as a ready explanation is provided with the answers and thus brings home to the student the importance of reading the question very carefully and not mistaking, say, nitrogen for nitrous oxide; however, a good examination committee would not permit their inclusion. The authors' introduction gives general advice to the prospective candidate and advises how MCQ papers are marked and the range of scores a candidate needs to achieve. However, the authors fail to mention a not uncommon problem, that the candidate fails to leave enough time to transpose his answers to the computer marking cards. Perhaps a future edition might include some of these cards so that the candidate can practise?

No doubt the questions in this book have been tried out in the authors' own departments, so it would have been interesting to have known what the statistical analysis of the answers to these questions reveals. In professional MCQ examinations, statistical tests are used to establish if a question is a good discriminator (i.e. a "good" question) or if a poor response by candidates shows the question to be poor, ambiguous or too difficult. The value of such analysis is that not only may poor whole questions be identified easily, but any problems inherent in the five individual responses to the stem can also be spotted, thus permitting subsequent correction. A selection of questions which are highly discriminatory are often re-run at subsequent examinations to provide an internal standard by which the pass mark and banding thresholds may be adjusted. By the same token, questions which are "far too easy" may be readily identified. This approach enables a balanced overall paper to be set by examiners.

This book fulfils a second purpose, since knowledge of the contents of the primary anaesthetic textbook can be tested by the student for himself. Students will appreciate this book, which is pleasingly produced and modestly priced.

A. P. Adams

Plasma Volume Expansion. Edited by J.-F. Baron. Published (1992) by Arnette–Blackwell, Paris. Pp. 233; illustrated. Price £42.50.

This is a multiauthor monograph which considers the physiological basis of plasma and tissue volume regulation, the pharmacology of colloid solutions and the choice of plasma substitute in various clinical fields.

The book suffers from repetition, each of the first five chapters presenting Starling's equation, albeit in slightly different forms. The standard of proof reading is very poor and there are many "howlers", for example "dies" instead of "dyes" (p. 1), "secondaryly" (p. 165) and "a big french hospital" (p. 161). One could fill many pages with similar examples of spelling and grammatical errors. Unfortunately, in some instances this becomes a serious barrier to understanding.

Despite this, however, the book contains a lot of information on a topic which is covered only superficially in standard textbooks. The chapters on interstitial volume regulation and lymphatic clearance, mechanisms of pulmonary oedema and the four clinical chapters at the end are particularly good and will repay study by any anaesthetist involved in intensive care, cardiac surgery or organ transplantation. There is, however, no consideration of fluid transfer in neonates, young children or in pregnancy. Some of the chapters are highly technical and likely to appeal only to those who have specialist knowledge outside that of most anaesthetists. Inexcusably, there is no index.

J. P. H. Fee

AUTHOR INDEX

VOLUME 69, 1992

British Journal of Anaesthesia

ARS = Anaesthetic Research Society papers
C = Correspondence
E = Editorial
R = Book review

Ackerman, W. E. *see* Andrews, P. J. D. 401–403
Ackers, J. W. L. *see* Palazzo, M. G. A., (*ARS*) 530P
Adkisson, G. H. Spread of spinal anaesthesia, (*C*) 328
Adt, M. Atracurium and histamine, (*C*) 110
Aggarwal, S. *see* Cook, D. R. 580–585
Agoston, S. *see* Werba, A. 382–386
Aitkenhead, A. R. *see* Fell, D., (*R*) 667–668
Akhtar, T. M. *see* Keenan, G. M. A., (*ARS*) 533P
Alcon, A. *see* Escolano, F. 404–406
Allardyce, W. *see* Haynes, S. R. 599–601
Amaha, K. *see* Oshima, T. 236–239
Ambakederemo, A. W. *see* Hopkins, P. M., (*ARS*) 210–211P
Anderson, F. M. *see* Philips, B. J. 407–408
Anderton, J. *see* Eddleston, J. M. 154–158
Andrews, P. J. D., Ackerman, W. E., Juneja, M., Cases-Cristobal, V. and Rigor, B. M. Transient bradycardia associated with extradural blood patch after inadvertent dural puncture in parturients 401–403
Andrews, P. L. R. Physiology of nausea and vomiting: speculations on the mechanisms of postoperative nausea and vomiting 2–19S
Angster, R. *see* Nebauer, A. E. 58–60
Ansermino, J. M. and Blogg, C. E. Cricoid pressure may prevent insertion of the laryngeal mask airway 465–467
Anthony, J. M. *see* Kapadia, F. 640–642
Armstrong, P. *see* Philips, B. J. 407–408
Armstrong, P. J., Cullen, M. and Scott, D. H. T. The Siterite ultrasound machine: an aid to internal jugular vein cannulation? (*ARS*) 533–534P
Armstrong, P. J. *see* Morton, C. P. J., (*ARS*) 533P
Artigas, A., Lemaire, F., Suter, P. M. and Zapol, W. M., (editors) *Adult Respiratory Distress Syndrome*, (*R*) 427
Asbury, A. J. *see* O'Donnell, N. G. 70–74
Atcheson, R., Lambert, D. G. and Rowbotham, D. J. Fentanyl inhibits evoked [^{3}H]noradrenaline release from human neuroblastoma cells, (*ARS*) 531P
Atkinson, R. *see* Murphy, P. G., (*ARS*) 532–533P
Aune, H. *see* Pettersen, B. 204–205; (*C*) 665

Baliga, N. *see* Bethune, D. W., (*C*) 665
Ball, G. and Bohaychuck, W. *Standard Operating Procedures for Investigators*, (*R*) 231
Ball, S. P., Dorkins, H. R., Ellis, F. R., Hall, J. L., Halsall, P. J., Hopkins, P. M. and Stewart, A. D. Is muscle biopsy for malignant hyperthermia diagnosis still necessary? (*ARS*) 222–223P
Ballesteros, M. *see* Boldt, J. 45–50
Baraka, A. Onset of neuromuscular block in myasthenic patients, (*C*) 227–228
Barker, I. *see* Michael, S. 577–579
Barker, P., Langton, J. A., Murphy, P. J. and Rowbotham, D. J. Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway 314–315
Barker, P., Langton, J. A., Wilson, I. G. and Smith, G. Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol 23–25
Barker, P. *see* Langton, J., (*C*) 661–662; Rabey, P. G. 346–348; Trotter, T. N. 352–355
Barker, S. J. *see* Thomas, A. N., (*ARS*) 527–528P
Baron, J.-F., (editor) *Plasma Volume Expansion*, (*R*) 668
Barrie, J. R., Beatty, P. C. W., Campbell, I. T. and Healy, T. E. J. Determination of the onset of rebreathing: comparison of six methods during spontaneous ventilation, (*ARS*) 527P
Baskett, P. J. F. Advances in cardiopulmonary resuscitation 182–193
Batchelor, A. M. and Conacher, I. D. Anaphylactoid or carcinoid? 325–327
Baxter, M. K. *see* Nolan, K. M. 194–196
Beatty, P. C. W., Burgess, H. M. and Healy, T. E. J. Breakdown of halogenated inhalation anaesthetic agents with water vapour in breathing systems, (*ARS*) 216P
Beatty, P. C. W., Meakin, G. and Healy, T. E. J. Fractional delivery of fresh gas: a new index of the efficiency of semi-closed breathing systems 474–477
Beatty, P. C. W. *see* Barrie, J. R., (*ARS*) 527P; Willard, T. B., (*ARS*) 213P
Becquemin, J.-P. *see* Beydon, L. 137–142
Bedford, R. F. *see* Veselis, R. A. 246–254
Bell, C., Hughes, C. W. and Oh, T. H., (editors) *The Pediatric Anesthesia Handbook*, (*R*) 230
Bembridge, J. *see* Bennett, M. W. R., (*ARS*) 220P
Bengtson, J. P., Haraldsson, A., Bengtsson, A., Henriksson, B.-A. and Stenqvist, O. Inspiratory to end-tidal oxygen difference, (*C*) 663
Bengtsson, A. *see* Bengtson, J. P., (*C*) 663
Benhamou, D. *see* Veroli, P. 461–464
Bennett, M. W. R., Shah, M. V. and Bembridge, J. Effect of four different maintenance anaesthetic techniques for minor surgery on gastric emptying, (*ARS*) 220P
Bergesio, R. *see* Thomas, A. N., (*ARS*) 527–528P
Berridge, J. C. Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation 409–410
Berry, A. M. *see* McDonald, P. F. 399–400
Berry, C. B. and Morton, N. S. Venous sequelae of diclofenac, (*C*) 332
Berthoud, M. *see* Peacock, J. E. 363–367
Bethune, D. W. and Baliga, N. Skin injury with a pulse oximeter, (*C*) 665
Bethune, D. W., Ghosh, S., Gray, B., Kerr, L., Walker, I. A., Doolan, L.A., Harwood, R. J. and Sharples, L. D. Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion 197–199
Beydon, L., Hassapopoulos, J., Quera, M.-A., Rauss, A., Becquemin, J.-P., Bonnet, F., Harf, A. and Goldenberg, F. Risk factors for oxygen desaturation during sleep, after abdominal surgery 137–142
Bhatt, S. B., Hutchinson, R. C., Tomlinson, B., Oh, T. E. and Mak, M. Effect of dobutamine on oxygen supply and uptake in healthy volunteers 298–303
Bisbe, E. *see* Escolano, F. 404–406
Blogg, C. E. *see* Ansermino, J. M. 465–467
Blumgart, C. H., Ryall, D., Dennison, B. and Thompson-Hill, L. M. Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic 457–460
Bohaychuck, W. *see* Ball, G., (*R*) 231
Boldt, J., Knothe, C., Zickmann, B., Ballesteros, M., Russ, W., Dapper, F. and Hempelmann, G. The role of enoximone in cardiac surgery 45–50
Bonnet, F. *see* Beydon, L. 137–142
de Boo, T. *see* Vanlinthout, L. E. H. 29–35
Booij, L. H. D. J. *see* Hull, J. M., (*ARS*) 534P; Vanlinthout, L. E. H. 29–35
Booth, J. V. *see* Smith, D. C., (*ARS*) 223P
Borgeat, A. *see* Wilder-Smith, O. H. G., (*C*) 663–664
Bosnjak, Z. J. *see* Flynn, N. M., (*ARS*) 210P
Bossaert, L. L. *see* Heytens, L. 87–91
Bouchier-Hayes, D. *see* Ryan, T. 101–104
Boules, Z. *see* Cooper, R. 269–273
Boulton, A. J. M. *see* Vohra, A., (*ARS*) 212–213P
Boyd, A. H. *see* Martin, C. S., (*ARS*) 526P
Boyd, S. G. *see* Mason, D. G. 562–566; 567–569
Boylan, M. K. G. *see* Columb, M. O., (*ARS*) 211P
Boyle, E. *see* Griffiths, R., (*ARS*) 530P
Brand, C. *see* Lange, H. 478–481
Bras, P. and Ponte, J. Where is the bobbin? (*ARS*) 539P
Brauer, S. D. *see* Jacobsen, W. K., (*R*) 333–334
Bricard, H. *see* Laroche, D. 611–614

Briegel, J. *see* Welte, M. 637–639
Brighouse, D. and Guard, B. Anaesthesia for Caesarean section in a patient with Ehlers–Danlos syndrome type IV 517–519
Britt, R. P. *see* Samsoon, G. 653–656
Bromage, P. R. Bleeding time, (*C*) 330
Brown, A. C. D. and Norton, M. L. *Atlas of the Difficult Airway*, (*R*) 231
Brown, D. L. *Atlas of Regional Anaesthesia*, (*R*) 426
Browne, B. L., Prys-Roberts, C. and Wolf, A. R. Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia 570–576
Brownridge, P. *see* McMenemin, I. M. 417–419
Bunce, K. T. and Tyers, M. B. The role of 5-HT in postoperative nausea and vomiting 60–62S
Burgess, H. M. *see* Beatty, P. C. W., (*ARS*) 216P
Burgess, N. A. *see* Scriven, M. W., (*C*) 422–423
Burgmann, H. *see* Reckendorfer, H. 288–291
Burke, D. J. *see* Hicks, R. G. 130–136
Butler, P. J. Recognition and management of difficult airway problems, (*C*) 225

Calder, I. Recognition and management of difficult airway problems, (*C*) 224
Cameron, R. J. *see* Merry, A. F. 92–94
Campbell, I. T. Dual publication of abstracts, (*C*) 227
Campbell, I. T. *see* Barrie, J. R., (*ARS*) 527P
Campkin, N., Ooi, R. and Soni, N. Oxygen uptake during rebreathing in a Mapleson A system, (*ARS*) 538P
Campkin, N. *see* Hood, J. R., (*ARS*) 535P
Campkin, N. T. A., Hood, J. R. and Feldman, S. A. Fade during recovery from vecuronium, (*C*) 226–227
Camu, F. *see* Verborgh, C. 36–39
Caria, M. A. *see* De Riu, P. L. 177–181
Carli, F. *see* McHale, S. 634–636
Carrie, L. E. S. Metallic fragments and the combined spinal–extradural technique, (*C*) 662–663
Carson, R. J. and Reynolds, F. Elimination of bupivacaine and pethidine from the rabbit feto–placental unit 150–153
Cases-Cristobal, V. *see* Andrews, P. J. D. 401–403
Cashman, J. *see* Price, M. L. 172–176
Castaño, J. *see* Escolano, F. 404–406
Chambers, W. A. Peripheral nerve damage and regional anaesthesia, (*E*) 429–430
Chambers, W. A. *see* Ronald, A. L. 105–107
Charlett, A. *see* Landon, M. J. 81–86
Charlton, A. J. *see* Vohra, A., (*ARS*) 212–213P
Charlton, G. A., Sedgwick, J. and Sutton, D. N. Anaesthetic management of renin secreting nephroblastoma 206–209
Chaudhri, S., Colvin, J. R., Todd, J. G. and Kenny, G. N. C. Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma 607–610
Chen, B.-J. *see* Tsai, S. K. 255–258
Childs, D. *see* Martin, C. S., (*ARS*) 526P
Chraemmer-Jørgensen, B. *see* Olsen, K. S. 263–268
Chui, P. T. *see* Short, T. G. 162–167
Cigarini, I. *see* Joris, J. 341–345
Clanachan, A. S. *see* Finegan, B. A. 492–497
Clarke, R. S. J. *see* Cooper, R. 269–273; McCarthy, G., (*ARS*) 213–214P; McClune, S. 240–245
Cobley, M. and Vaughan, R. S. Recognition and management of difficult airway problems, (*C*) 225
Cody, M. W. and Johnston, J. A. Antenatal assessment for anaesthesia, (*C*) 332
Coe, A. J. and Moore, J. K. Intrathecal morphine-6-glucuronide and bupivacaine for postoperative pain, (*ARS*) 221P
Cohendy, R., Lefrant, J. Y., Laracine, M., Rebiere, T. and Eledjam, J. J. Effect of fentanyl on ventilatory resistances during barbiturate general anaesthesia 595–598
Cole, D. J. *see* Jacobsen, W. K., (*R*) 333–334
Collett, B. J. *see* Elliott, R. H., (*C*) 422
Columb, M. O., Murphy, P. G., Kowolik, M. J., Shah, M. V. and Boylan, M. K. G. Influence of myocardial preservation technique on perioperative neutrophil activity in patients undergoing coronary artery graft surgery, (*ARS*) 211P
Columb, M. O. *see* Murphy, P. G., (*ARS*) 532–533P
Colvin, J. R. *see* Chaudhri, S. 607–610
Conacher, I. D. *see* Batchelor, A. M. 325–327
Cook, D. R., Freeman, J. A., Lai, A. A., Kang, Y., Stiller, R. L., Aggarwal, S., Harrelson, J. C., Welch, R. M. and Samara, B. Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure 580–585
Cook, L. B. and Varley, S. Fatal tracheal compression after haemorrhage into the axilla 322–324
Cooper, R., Mirakhur, R. K., Clarke, R. S. J. and Boules, Z. Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium 269–273
Cooper, R. *see* McCarthy, G. J. 281–283
Cowan, B. *see* Haynes, S. R. 599–601
Cox, D. J. A. *see* Mallett, S. V. 307–313
Cozanitis, D. A. Probable resistance to vecuronium involving the 17-hydroxy metabolite, (*C*) 110–111
Crawford, M. R. *see* Hicks, R. G. 130–136
Creagh-Barry, P. *see* Landon, M. J. 81–86
Crosby, D. L., Rees, G. A. D. and Seymour, D. G., (editors) *The Ageing Surgical Patient—Anaesthetic, Operative and Medical Management*, (*R*) 426–427
Cullen, M. *see* Armstrong, P. J., (*ARS*) 533–534P
Cumming, A. D. *see* Power, I. 451–456
Cunningham, A. J. *see* Ryan, T. 101–104
Czech, T. *see* Werba, A. 382–386

Dahl, A. *see* Dahl, J. B., (*C*) 424–425
Dahl, J. B., Erichsen, C. J., Fuglsang-Frederiksen, A. and Kehlet, H. Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers 117–121
Dahl, J. B., Hansen, B. L., Hjortsø, N.-C., Erichsen, C. J., Møiniche, S. and Kehlet, H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery 4–8; Pre-emptive extradural analgesia, (*C*) 664–665
Dahl, J. B., Kehlet, H., Dierking, G., Dahl, A. and Kanstrup, J. Effect of preoperative opioid administration on postoperative pain, (*C*) 424–425
Dang, P. T. *see* Thomas, A. N. 397–398
Dapper, F. *see* Boldt, J. 45–50
Darke, P. G. G. *see* Young, L. E., (*ARS*) 222P
Day, P. *see* Murphy, P. G., (*ARS*) 532–533P
De Andrés, J. A. A puncture technique for continuous subarachnoid block, (*C*) 544–545
De Groote, D. *see* Joris, J. 341–345
Delooz, H. H., (editor) *Emergency Medicine and the Anaesthetist* (*Baillière's Clinical Anaesthesiology* series), (*R*) 546
Dennison, B. *see* Blumgart, C. H. 457–460
Derbyshire, D. R. *see* Fell, D., (*R*) 667–668
De Riu, P. L., Petruzzi, V., Testa, C., Mulas, M., Melis, F., Caria, M. A. and Mameli, O. Propofol anticonvulsant activity in experimental epileptic status 177–181
Desborough, J. P., Jones, P. M., Persaud, S. J., Landon, M. J. and Howell, S. L. Isoflurane inhibits insulin secretion from isolated rat pancreatic islets of Langerhans, (*ARS*) 532P
Desborough, J. P. *see* Hall, G. M., (*E*) 337–338
Devlin, J. C., Head-Rapson, A. G., Parker, C. J. R. and Hunter, J. M. Pharmacodynamics of mivacurium chloride in the cirrhotic patient, (*ARS*) 534–535P
Devlin, J. C., Phillips, B. J., Hunter, J. M. and Parker, C. J. R. Influence of body weight and gender on the pharmacodynamics of atracurium, (*ARS*) 217–218P
Dhamee, M. S. and Ghandi, S. K. Cardiovascular responses to tracheal extubation, (*C*) 229
Dhara, S. S. Retrograde intubation—a facilitated approach 631–633
Diedericks, J. *see* Puttick, R. M. 375–381
Dierking, G. *see* Dahl, J. B., (*C*) 424–425
Dierks, T. *see* Engelhardt, W. 75–80
Dige-Petersen, H. *see* Olsen, K. S. 263–268
Dodd, F. M., Simon, E. and McKeown, D. Effect of a cervical collar on the tidal volume of anaesthetized adult patients, (*ARS*) 526–527P
Doenicke, A. *see* Mayer, M. 511–512; Nebauer, A. E. 58–60
Donaghey, S. F. O'B. *see* Laycock, G. J. A. 356–362
Donaldson, M. D. J., Seaman, M. J. and Park, G. R. Massive blood transfusion 621–630
Doolan, L.A. *see* Bethune, D. W. 197–199
Doré, C. J. *see* Newton, D. E. F. 122–129
Dorkins, H. R. *see* Ball, S. P., (*ARS*) 222–223P
Dottrens, M., Rifat, K. and Morel, D. R. Comparison of extradural administration of sufentanil, morphine and sufentanil–morphine combination after Caesarean section 9–12
Downs, J. *see* Grenvik, A., (*R*) 334
Dresner, M. *see* Wood, P. R. 202–203
Drummond, G. B. *see* Nimmo, A. F., (*ARS*) 539–540P
Dubois, F. *see* Laroche, D. 611–614

Eddleston, J. M., Maresh, M., Horsman, E. L., Young, H., Lacey, P. and Anderton, J. Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia 154–158
Edmondson, W. C. *see* Peacock, J. E. 363–367
van Egmond, J. *see* Vanlinthout, L. E. H. 29–35
Eldor, J. Metallic fragments and the combined spinal–extradural technique, (*C*) 663
Eledjam, J. J. *see* Cohendy, R. 595–598
Elliott, P. *see* McCarthy, G., (*ARS*) 213–214P
Elliott, R. H. and Collett, B. J. Delayed septicaemia after extradural steroid treatment, (*C*) 422
Ellis, F. R., Halsall, P. J. and Hopkins, P. M. Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? 468–470
Ellis, F. R. *see* Ball, S. P., (*ARS*) 222–223P; Halsall, P. J. 471–473; Hopkins, P. M., (*ARS*) 531–532P
El Mikatti, N., Luthra, A. D., Healy, T. E. J. and Mortimer, A. J. Gastric regurgitation during general anaesthesia in the supine position with the laryngeal and face mask airways, (*ARS*) 529–530P
Engelhardt, W., Friess, K., Hartung, E., Sold, M. and Dierks, T. EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism 75–80
Entwistle, M. D., Sommerville, D. and Jones, J. G. Effect of brief hypoxaemia on the resting ECG in patients with exercise-induced cardiac ischaemia, (*ARS*) 536–537P
Erichsen, C. J. *see* Dahl, J. B. 4–8; 117–121; (*C*) 664–665
Erskine, R. J., Murphy, P. J., Langton, J. A. and Smith, G. Effect of age on the sensitivity of upper airway reflexes, (*ARS*) 538–539P
Escolano, F., Castaño, J., Lopez, R., Bisbe, E. and Alcon, A. Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery 404–406
Esener, Z., Sarihasan, B., Güven, H. and Üstün, E. Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum 586–588
Evans, F. E. *see* Mettam, I. M. 420–421
Evans, R. D. *see* Palazzo, M. G. A., (*ARS*) 530P

Faust, R. J., (editor) *Anesthesiology Review*, (*R*) 230–231
Fauvel, N. *see* Hood, J., (*ARS*) 218P
Fawcett, W. and Feldman, S. Comparison of recovery index of Org 9426 with simultaneous administration of pancuronium in the isolated arm compared with vecuronium and pancuronium, (*ARS*) 218P
Fee, J. P. H. *see* Ganta, R. 316–317
Feigl, W. *see* Reckendorfer, H. 288–291
Feldman, S. *see* Fawcett, W., (*ARS*) 218P; Hood, J., (*ARS*) 218P
Feldman, S. A. *see* Campkin, N. T. A., (*C*) 226–227; Hood, J. R., (*ARS*) 535P
Fell, D., Derbyshire, D. R., Aitkenhead, A. R. and Smith, G. *MCQ Companion to the Textbook of Anaesthesia*, (*R*) 667–668
Fell, D. and Lowrie, A. Cardiovascular responses to tracheal extubation, (*C*) 229
Fergusson, S. *see* Philips, B. J. 407–408
Finegan, B. A., Whiting, R. W., Tam, Y. K. and Clanachan, A. S. Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs 492–497
Fink, B. R. Vocal cord movement on induction of anaesthesia, (*C*) 661
Fink, B. R. *see* Pirogoff, N., (*R*) 333
Fischer, H. B. J. *see* Scott, P. V., (*C*) 108
Fletcher, R. Auto-PEEP, lung volume and sternotomy, (*ARS*) 527P; Bedside respiratory measurements with the Siemens–Elema CO_2 Analyzer, (*C*) 227
Flynn, N. M., O'Toole, D. P., Bosnjak, Z. J. and Kampine, J. P. Halothane produces potent endothelium-independent vasodilatation in canine middle cerebral arteries, (*ARS*) 210P
Foëx, P. *see* Muir, A. D., (*ARS*) 540P; Puttick, R. M. 375–381
Ford, J. L. *see* Lee, M. G. 522–525
Forrler, M. *see* Lleu, J. C., (*C*) 542
Fragen, R. J., (editor) *Drug Infusions in Anesthesiology*, (*R*) 112
Franchimont, P. *see* Joris, J. 341–345
Fraser, R. B. *see* Magides, A. D., (*ARS*) 529P
Freeman, J. A. *see* Cook, D. R. 580–585
Frenkel, C. and Urban, B. W. Molecular actions of racemic ketamine on human CNS sodium channels 292–297
Frid, I. *see* Wennberg, E. 13–18
Friess, K. *see* Engelhardt, W. 75–80
Frith, C. D. *see* Newton, D. E. F. 122–129
Fuglsang-Frederiksen, A. *see* Dahl, J. B. 117–121
Fulton, B. *see* Park, G., (*R*) 548

Ganta, R. and Fee, J. P. H. Pain on the injection of propofol: comparison of lignocaine with metoclopramide 316–317
Garrard, C. S. *see* Howell, S., (*ARS*) 536P
Gataure, P. S., Latto, I. P. and Taylor, H. Use of suction catheters as an alternative to tracheal tubes in adults 657–658
Geeurickx, A. *see* Wee, M. Y. K. 411–413
George, K. A. *see* Wright, P. M. C., (*ARS*) 219–220P
Gérard, J.-L. *see* Laroche, D. 611–614
Ghandi, S. K. *see* Dhamee, M. S., (*C*) 229
Ghosh, S. *see* Bethune, D. W. 197–199
Gill, R. S. and Scott, R. P. F. Etomidate shortens the onset time of neuromuscular block 444–446
Gillies, G. W. A. Hypoxaemia and insertion of the laryngeal mask airway, (*C*) 661
Gilly, H. *see* Werba, A. 382–386
Glen, J. B. *see* Puttick, R. M. 375–381; Taylor, I. N. 168–171
Goldenberg, F. *see* Beydon, L. 137–142
Goldfrank, L. R. *see* Hoffman, R. S., (*R*) 547
Goldhill, D. R. *see* Nolan, K. M. 194–196; (*ARS*) 214–215P; Taylor, T. H., (*R*) 334
Gopinath, R. Venous sequelae of diclofenac, (*C*) 332
Graham, S. G. The National Confidential Enquiry into Perioperative Deaths 1990, (*E*) 431–432
Gray, B. *see* Bethune, D. W. 197–199
Grenvik, A., Downs, J., Räsänen, J. and Smith, R., (editors) *Mechanical Ventilation and Assisted Respiration*, (*R*) 334
Griffiths, R., Norman, R. I., Boyle, E. and Rowbotham, D. J. Effect of halothane on [^{3}H]methylcholine uptake into rat brain synaptosomes, (*ARS*) 530P
Griffiths, R. W. *see* Michael, S. 577–579
Grimes, A. *see* Williams, N. J., (*C*) 228
Groh, J. *see* Welte, M. 637–639
Grounds, M. *see* Price, M. L. 172–176
Guard, B. *see* Brighouse, D. 517–519
Guéant, J.-L. *see* Laroche, D. 611–614
Gupta, A., Vegfors, M. and Lennmarken, C. Midazolam and cardioversion, (*C*) 422
Güven, H. *see* Esener, Z. 586–588

Haimerl, E. *see* Welte, M. 637–639
Haljamäe, H. *see* Wennberg, E. 13–18
Hall, G. M. and Desborough, J. P. Interleukin-6 and the metabolic response to surgery, (*E*) 337–338
Hall, J. L. *see* Ball, S. P., (*ARS*) 222–223P
Halsall, P. J., Ellis, F. R. and Knowles, P. F. Evaluation of spin resonance spectroscopy of red blood cell membranes to detect malignant hyperthermia susceptibility 471–473
Halsall, P. J. *see* Ball, S. P., (*ARS*) 222–223P; Ellis, F. R. 468–470; Hopkins, P. M., (*ARS*) 531–532P
Hanning, C. D. Prolonged postoperative oxygen therapy, (*E*) 115–116
Hansen, B. L. *see* Dahl, J. B. 4–8; (*C*) 664–665
Haraldsson, Å. *see* Bengtson, J. P., (*C*) 663
Harf, A. *see* Beydon, L. 137–142
Harrelson, J. C. *see* Cook, D. R. 580–585
Harris, K. The role of prostaglandins in the control of renal function, (*E*) 233–235
Harrison, D. A. and Langham, B. T. Postdural puncture headache in urological surgery: an evaluation of the atraumatic spinal needle, (*ARS*) 540–541P
Harrison, D. A. *see* Langham, B. T., (*ARS*) 537–538P
Hartung, E. *see* Engelhardt, W. 75–80
Harwood, R. J. *see* Bethune, D. W. 197–199
Hashimoto, Y. *see* Koga, Y. 65–69
Hassapopoulos, J. *see* Beydon, L. 137–142
Hatch, D. J., Saul, C., Wilson, L. E. and Rehder, K. Action of ketamine on isolated porcine trachealis muscle, (*ARS*) 217P
Haynes, S. R., Allardyce, W., Cowan, B. and Tansey, P. Accuracy of coagulation studies performed on blood samples obtained from arterial cannulae 599–601
Head-Rapson, A. G. *see* Devlin, J. C., (*ARS*) 534–535P; Ralston, S. J., (*ARS*) 220–221P
Healy, T. E. J. *see* Barrie, J. R., (*ARS*) 527P; Beatty, P. C. W., (*ARS*) 216P; 474–477; El Mikatti, N., (*ARS*) 529–530P; Wang, D. Y., (*ARS*) 221–222P
Heath, M. L. Recognition and management of difficult airway problems, (*C*) 224–225
Hempelmann, G. *see* Boldt, J. 45–50
Henderson, P. *see* Michael, S. 577–579
Henriksen, L. *see* Olsen, K. S. 263–268
Henriksson, B.-Å. *see* Bengtson, J. P., (*C*) 663

Henze, T. *see* Stephan, H. 51–57
Herold, M. *see* Putensen, C. 513–516
Herz, A. *see* Welte, M. 637–639
Heytens, L., Martin, J. J. and Bossaert, L. L. *In vitro* diagnosis of malignant hyperthermia: influence of electrical stimulation on the contracture response to caffeine 87–91
Hickman, J. A. *see* Tolley, P. M. 320–321
Hicks, R. G., Woodforth, I. J., Crawford, M. R., Stephen, J. P. H. and Burke, D. J. Some effects of isoflurane on I waves of the motor evoked potential 130–136
Higgins, D. *see* Mason, D. G. 562–566; 567–569
Hjortsø, N.-C. *see* Dahl, J. B., 4–8; (*C*) 664–665
Hoernecke, R. *see* Nebauer, A. E. 58–60
Hoffman, R. S. and Goldfrank, L. R., (editors) *Critical Care Toxicology* (*Contemporary Management in Critical Care* series), (*R*) 547
Hofmann, A. *see* Mayer, M. 511–512
Hood, J., Fauvel, N. and Feldman, S. Effect of administration of vecuronium on recovery from pancuronium and *vice versa*, (*ARS*) 218P
Hood, J. R., Campkin, N. and Feldman, S. A. Influence of circulating drug on recovery of neuromuscular block in the isolated forearm, (*ARS*) 535P
Hood, J. R. *see* Campkin, N. T. A., (*C*) 226–227
Hooper, J. *see* Oxorn, D. C. 200–201
Hopkins, P. M., Ellis, F. R. and Halsall, P. J. Inhibition of sodium–calcium exchange increases skeletal muscle contracture response to halothane, (*ARS*) 531–532P
Hopkins, P. M., Yar, T., Spencer, G.E., Ambakederemo, A. W. and Winlow, W. Halothane-induced changes in intracellular calcium ion concentration in neurones from *Lymnaea stagnalis*, (*ARS*) 210–211P
Hopkins, P. M. *see* Ball, S. P., (*ARS*) 222–223P; Ellis, F. R. 468–470
Horrocks, M. *see* Kaneko, K., (*ARS*) 537P
Horsman, E. L. *see* Eddleston, J. M. 154–158
Howell, S., Wanigasekera, V., Sear, J. W. and Garrard, C. S. Heart rate spectrum analysis during induction of anaesthesia with thiopentone or propofol, (*ARS*) 536P
Howell, S. L. *see* Desborough, J. P., (*ARS*) 532P
Howsam, S. *see* McHale, S. 634–636
Huang, Y. F., Upton, R. N., Rutten, A. J. and Runciman, W. B. I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects on circulatory function 368–374
Hughes, C. W. *see* Bell, C., (*R*) 230
Hull, C. J. *see* Sykes, M. K., (*R*) 666
Hull, J. M., Robertson, E. N., Booij, L. H. D. J. and Verbeek, A. M. Effect of rocuronium and vecuronium on intraocular pressure, (*ARS*) 534P
Hunt, P. B. *see* Lee, M. G. 522–525
Hunter, D. *see* Madej, T. H. 554–557; Wheatley, R. G. 558–561
Hunter, J. M. *see* Devlin, J. C., (*ARS*) 217–218P; (*ARS*) 534–535P; Parker, C. J. R. 274–280; 439–443
Hutchinson, R. C. *see* Bhatt, S. B. 298–303
Hyatt, J. *see* Thomas, A. N. 397–398; (*ARS*) 527–528P

Ikeda, K. *see* Katoh, T. 259–262
Imray, I. McG., Reid, T. M. S. and Noble, D. W. Radioimmunoassay tests and anaphylaxis, (*C*) 543–544
Inglis, T. Bacterial overgrowth and gastric dysfunction, (*C*) 545
Ip Yam, C. and Wood, P. Repeated resistance to non-depolarizing neuromuscular blocking drugs in a patient with multiple myeloma, (*C*) 111
Ireland, D. S. *see* Lee, M. G. 522–525
Iwatsuki, N. *see* Koga, Y. 65–69

Jackson, I. J. B. *see* Madej, T. H. 554–557; Wheatley, R. G. 558–561
Jacobsen, W. K., Lobo, D. P., Cole, D. J. and Brauer, S. D., (editors) *Manual of Post-Anesthesia Care*, (*R*) 333–334
Jacquet, N. *see* Joris, J. 341–345
James, M. F. M. *see* Lamb, K. 143–147
Janicki, P. K. *see* Lamb, K. 143–147
Jedeikin, R., Olsfanger, D., Shachor, D. and Mansoor, K. Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis 349–351
Jensen, K. A. *see* Nissen, I. 304–306
Johnston, J. A. *see* Cody, M. W., (*C*) 332
Jones, J. G. *see* Entwistle, M. D., (*ARS*) 536–537P; Myers, D. S., (*ARS*) 222P; Sapsford, D. J., (*ARS*) 538P; (*ARS*) 541P
Jones, M. R. *see* Ngan Kee, W. D. 647–652
Jones, P. M. *see* Desborough, J. P., (*ARS*) 532P
Jones, R. M. *see* Kenna, J. G., (*C*) 228–229
Jones, R. P. Insulated regional block needles, (*C*) 423–424
Jones, R. S. *see* Young, L. E., (*ARS*) 222P
Jordan, C. *see* Newton, D. E. F. 122–129
Joris, J., Cigarini, I., Legrand, M., Jacquet, N., De Groote, D., Franchimont, P. and Lamy, M. Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy 341–345
Joshi, G. *see* McSwiney, M., (*C*) 331–332
Juneja, M. *see* Andrews, P. J. D. 401–403

Kaldas, R. *see* Notcutt, W. G. 95–97
Kampine, J. P. *see* Flynn, N. M., (*ARS*) 210P
Kaneko, K., Prys-Roberts, C., Nevin, M., Magee, T. R. and Horrocks, M. Comparison of the effects of methoxamine and phenylephrine on middle cerebral artery velocity during carotid endarterectomy, (*ARS*) 537P
Kang, Y. *see* Cook, D. R. 580–585
Kanstrup, J. *see* Dahl, J. B., (*C*) 424–425
Kapadia, F., Shelly, M. P., Anthony, J. M. and Park, G. R. An active heat and moisture exchanger 640–642
Kaplan, J. A., (editor) *Thoracic Anesthesia*, 2nd Edn, (*R*) 112
Kashyap, L. *see* Yaddanapudi, L. N., (*C*) 661
Kato, M. *see* Koga, Y. 65–69
Katoh, T., Suguro, Y., Nakajima, R., Kazama, T. and Ikeda, K. Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia 259–262
Katz, J., Kavanagh, B. P. and Sandler, A. N. Effect of preoperative opioid administration on postoperative pain, (*C*) 424
Kavanagh, B. P. *see* Katz, J., (*C*) 424
Kazama, T. *see* Katoh, T. 259–262
Kazmaier, S. *see* Stephan, H. 51–57
Keenan, G. M. A., Ruiz, K., Akhtar, T. M. and Shah, M. V. Patient-controlled analgesia after thoracotomy: thoracic extradural *vs* i.v. fentanyl, (*ARS*) 533P
Kehlet, H. *see* Dahl, J. B. 4–8; 117–121; (*C*) 424–425; (*C*) 664–665
Kenna, J. G. and Jones, R. M. A National Database on hepatitis after exposure to inhaled anaesthetics, (*C*) 228–229
Kenny, G. N. C. *see* Chaudhri, S. 607–610; Kinsella, J. 19–22; Russell, D. 63–68S; Taylor, I. N. 168–171
Kerr, L. *see* Bethune, D. W. 197–199
Kestin, I. G. Intrathecal diamorphine–bupivacaine during labour, (*C*) 108
Kinsella, J., Moffat, A. C., Patrick, J. A., Prentice, J. W., McArdle, C. S. and Kenny, G. N. C. Ketorolac trometamol for postoperative analgesia after orthopaedic surgery 19–22
Kirby, R. R. *see* Miller, R. D., (*R*) 113
Knight-George, A. B. *see* Samsoon, G. 653–656
Knothe, C. *see* Boldt, J. 45–50
Knowles, P. *see* Notcutt, W. G. 95–97
Knowles, P. F. *see* Halsall, P. J. 471–473
Knox, J. W. D. *see* Oxorn, D. C. 200–201
Koga, Y., Sato, S., Sodeyama, N., Takahashi, M., Kato, M., Iwatsuki, N. and Hashimoto, Y. Comparison of the relaxant effects of diazepam, flunitrazepam and midazolam on airway smooth muscle 65–69
Kongsgaard, U. *see* Pettersen, B. 204–205; (*C*) 665
Konieczko, K. M. *see* Newton, D. E. F. 122–129
Korttila, K. The study of postoperative nausea and vomiting 20–23S
Kowolik, M. J. *see* Columb, M. O., (*ARS*) 211P
Kumar, A. Y. *see* Shankar, K. B., (*C*) 542–543
Kumar, S. *see* Vohra, A., (*ARS*) 212–213P
Kwan, W.-F. *see* Tsai, S. K. 255–258

Lacey, P. *see* Eddleston, J. M. 154–158
Lai, A. A. *see* Cook, D. R. 580–585
Lamb, K., James, M. F. M. and Janicki, P. K. The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses 143–147
Lambert, D. G. *see* Atcheson, R., (*ARS*) 531P
Lamy, M. *see* Joris, J. 341–345
Landon, M. *see* Matson, A. M., (*ARS*) 528–529P
Landon, M. J., Creagh-Barry, P., McArthur, S. and Charlett, A. Influence of vitamin B_{12} status on the inactivation of methionine synthase by nitrous oxide 81–86
Landon, M. J. *see* Desborough, J. P., (*ARS*) 532P
Lange, H., Stephan, H., Brand, C., Zielmann, S. and Sonntag, H. Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery 478–481
Langham, B. T. and Harrison, D. A. Pressor response to venous cannulation and effect of local anaesthetic infiltration, (*ARS*) 537–538P

Langham, B. T. *see* Harrison, D. A., (*ARS*) 540–541P

Langton, J., Wilson, I., Barker, P. and Smith, G. Vocal cord movement on induction of anaesthesia, (*C*) 661–662

Langton, J. A. *see* Barker, P. 23–25; 314–315; Erskine, R. J., (*ARS*) 538–539P; Rabey, P. G. 346–348; Trotter, T. N. 352–355

Laorden, M. L. *see* Micol, J. A. 487–491

Laracine, M. *see* Cohendy, R, 595–598

Laroche, D., Lefrançois, C., Gérard, J.-L., Dubois, F., Vergnaud, M.-C., Guéant, J.-L. and Bricard, H. Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs 611–614

Laska, E. M. *see* Max, M. B., (*R*) 230

Latto, I. P. *see* Gataure, P. S. 657–658

Laurence, A. S. *see* Martlew, R., (*ARS*) 219P

Laverty, J. *see* Mahajan, R. P. 318–319

Lawes, E. G. *see* O'Kelly, S. W., (*C*) 330–331

Lawler, P. G. P. *see* Wood, P. R. 202–203

Laycock, G. J. A., Mitchell, I. M., Paton, R. D., Donaghey, S. F. O'B., Logan, R. W. and Morton, N. S. EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects 356–362

Lee, C. *see* Tsai, S. K. 255–258

Lee, M. G., Ford, J. L., Hunt, P. B., Ireland, D. S. and Swanson, P. W. Bacterial retention properties of heat and moisture exchange filters 522–525

Lefrançois, C. *see* Laroche, D. 611–614

Lefrant, J. Y. *see* Cohendy, R. 595–598

Legrand, M. *see* Joris, J. 341–345

Lemaire, F. *see* Artigas, A., (*R*) 427

Lennmarken, C. *see* Gupta, A., (*C*) 422

Lerman, J. Surgical and patient factors involved in postoperative nausea and vomiting 24–32S

Lerou, J. G. C. *see* Vanlinthout, L. E. H. 29–35

Lewis, I. H. and Sneyd, R. Propofol in uraemic patients, (*C*) 329

Lewis, M. H. *see* Scriven, M. W., (*C*) 422–423

Liddle, M. W. D. Damage to coaxial breathing systems, (*C*) 425

Lingnau, W. *see* Putensen, C. 513–516

Lleu, J. C., Forrler, M., Pottecher, T. and Otteni, J. C. Retrograde intubation using the subcricoid region, (*C*) 542

Lloyd-Thomas, A. R. *see* Mason, D. G. 562–566; 567–569

Lobo, D. P. *see* Jacobsen, W. K., (*R*) 333–334

Logan, R. W. *see* Laycock, G. J. A. 356–362

Lomholt, N. Tracheal models which simulate the compliance of the adult male trachea 98–100

Long, K. J. *see* Young, L. E., (*ARS*) 222P

Longnecker, D. E. and Murphy, F. L., (editors) *Dripps/Eckenhoff/Vandam Introduction to Anaesthesia*, 8th Edn, (*R*) 231

Lopez, R. *see* Escolano, F. 404–406

Lowrie, A. *see* Fell, D., (*C*) 229; Martlew, R., (*ARS*) 219P

Luff, N. P. *see* Newton, D. E. F. 122–129

Lunn, J. N. *Lecture Notes on Anaesthetics*, 4th Edn, (*R*) 113

Luthra, A. D. *see* El Mikatti, N., (*ARS*) 529–530P

McArdle, C. S. *see* Kinsella, J. 19–22

McArthur, S. *see* Landon, M. J. 81–86

McCaroll, M. *see* McSwiney, M., (*C*) 331–332

McCarthy, G. and Mirakhur, R. K. *MCQ for the Higher Examinations in Clinical Pharmacology*, (*R*) 546

McCarthy, G., Mirakhur, R. K., Clarke, R. S. J. and Elliott, P. Postoperative oxygenation in the elderly after ophthalmic surgery: comparison of local and general anaesthesia, (*ARS*) 213–214P

McCarthy, G. J., Cooper, R., Stanley, J. C. and Mirakhur, R. K. Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly 281–283

McClune, S., McKay, A. C., Wright, P. M. C., Patterson, C. C. and Clarke, R. S. J. Synergistic interaction between midazolam and propofol 240–245

McClure, J. H. *see* Morton, C. P. J., (*ARS*) 533P

McDonald, P. F. and Berry, A. M. Topical anaesthesia for extracorporeal shock wave lithotripsy 399–400

Macdonald, R. Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), (*C*) 109–110

McDonald, R. Bleeding time, (*C*) 329

McFie, A. G., Magides, A. D. and Reilly, C. S. Disposition of alfentanil in burns patients 447–450

McGoldrick, E., (editor) *Anaesthesia for Ophthalmic and Otolaryngologic Surgery*, (*R*) 667

McHale, S., Mitchell, V., Howsam, S. and Carli, F. Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour 634–636

McHale, S. P. and White, D. C. Control of carbon dioxide in circle systems, (*ARS*) 529P

McHale, S. P. *see* Wolff, A. H., (*ARS*) 539P

McKay, A. C. *see* McClune, S. 240–245

McKeown, D. *see* Dodd, F. M., (*ARS*) 526–527P

McLauchlan, G. A. *see* Peacock, J. E. 363–367

McLeod, D. *see* Vohra, A., (*ARS*) 212–213P

McMahon, S. B. *see* Rice, A. S. C. 433–438

McMenemin, I. M., Sissons, G. R. and Brownridge, P. Accidental subdural catheterization: radiological evidence of a possible mechanism for spinal cord damage 417–419

McMurray, T. J. *see* Phillips, A. S., (*ARS*) 211–212P

McQuay, H. J. Pre-emptive analgesia, (*E*) 1–3

McSharry, C. P. *see* O'Donnell, N. G. 70–74

McSwiney, M., Joshi, G. and McCaroll, M. Blood loss during total hip replacement, (*C*) 331–332

Madej, T. H., Wheatley, R. G., Jackson, I. J. B. and Hunter, D. Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia 554–557

Madej, T. H. *see* Wheatley, R. G. 558–561

Magee, T. R. *see* Kaneko, K., (*ARS*) 537P

Magides, A. D., Stanley, K. P., Fraser, R. B. and Reilly, C. S. A longitudinal study of gastric emptying of a test meal during pregnancy, (*ARS*) 529P

Magides, A. D. *see* McFie, A. G. 447–450

Mahajan, R. P. and Laverty, J. Lung function after vecuronium pretreatment in young, healthy patients 318–319

Mainzer, B. *see* Stühmeier, K. D. 602–606

Majors, K. *see* Myers, D. S., (*ARS*) 222P

Mak, M. *see* Bhatt, S. B. 298–303

Mallett, S. V. and Cox, D. J. A. Thrombelastography 307–313.

Mallick, A. *see* Yaddanapudi, L. N., (*C*) 661

Mameli, O. *see* De Riu, P. L. 177–181

Mansoor, K. *see* Jedeikin, R. 349–351

Maresh, M. *see* Eddleston, J. M. 154–158

Marino, P. *see* Veselis, R. A. 246–254

Marks, L. F. *see* Saddler, J. M. 26–28

Marsh, D. *see* Matta, B., (*ARS*) 215P

Marshall, I. G. *see* Tian, L. 284–287

Martin, C. S., Boyd, A. H. and Childs, D. Changes in respiratory function after laparoscopic cholecystectomy, (*ARS*) 526P

Martin, J. J. *see* Heytens, L. 87–91

Martlew, R., Lowrie, A. and Laurence, A. S. Four anaesthetic techniques for day-case oral surgery, (*ARS*) 219P

Mason, D. G., Higgins, D., Boyd, S. G. and Lloyd-Thomas, A. R. Effects of isoflurane anaesthesia on the median nerve somatosensory evoked potential in children 562–566; Sequential measurement of the median nerve somatosensory evoked potential during isoflurane anaesthesia in children 567–569

Mather, C., Raftery, S. and Prys-Roberts, C. Somatic movement and oesophageal motility during isoflurane anaesthesia 40–44

Matson, A. M., Landon, M., Royston, B. D., White, D. C. and Nunn, J. F. Components of the inspired to arterial isoflurane partial pressure difference, (*ARS*) 528–529P

Matta, B., Marsh, D. and Nevin, M. Laryngeal mask airway: a more successful method of insertion, (*ARS*) 215P

Max, M. B., Portenoy, R. K. and Laska, E. M., (editors) *Advances in Pain Research and Therapy, Volume 18: The Design of Analgesic Clinical Trials*, (*R*) 230

Mayer, M., Doenicke, A., Hofmann, A. and Peter, K. Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia 511–512

Mayer, M. *see* Nebauer, A. E. 58–60

Meakin, G. *see* Beatty, P. C. W. 474–477

Mehta, M. P. *see* Tian, L. 284–287

Melis, F. *see* De Riu, P. L. 177–181

Menck, S. *see* Stephan, H. 51–57

Merry, A. F., Wardall, G. J., Cameron, R. J., Peskett, M. J. and Wild, C. J. Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy 92–94

Mertzlufft, F. *see* Zander, R., (*R*) 333

Messeter, K. *see* Reinstrup, P. 615–620

Mettam, I. M., Reddy, T. R. and Evans, F. E. Life-threatening acute respiratory distress in late pregnancy 420–421

Michael, S., Barker, I., Henderson, P., Griffiths, R. W. and Reilly, C. S. Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery 577–579

Micol, J. A. and Laorden, M. L. Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat 487–491

Mikawa, K. *see* Yaku, H., (*C*) 225–226
Millar, B. *see* Price, M. L. 172–176
Miller, R. D., Kirby, R. R., Ostheimer, G. W., Roizen, M. F. and Stoetling, R. K., (editors) *Year Book of Anesthesia, 1991*, (*R*) 113
Mirakhur, R. K. *see* Cooper, R. 269–273; McCarthy, G., (*ARS*) 213–214P; (*R*) 546; McCarthy, G. J. 281–283; Phillips, A. S., (*ARS*) 211–212P
Mitchell, I. M. *see* Laycock, G. J. A. 356–362
Mitchell, V. *see* McHale, S. 634–636
Mizushima, A. The United Kingdom as seen by a Japanese Anaesthetist, (*C*) 108–109
Moffat, A. C. *see* Kinsella, J. 19–22
Møiniche, S. *see* Dahl, J. B. 4–8; (*C*) 664–665
Moodley, J. *see* Orlikowski, C. E. P. 159–161
Moore, J. K. *see* Coe, A. J., (*ARS*) 221P
Morel, D. R. *see* Dottrens, M. 9–12; Wilder-Smith, O. H. G., (*C*) 663–664
Mori, K. *see* Murayama, T. 61–64
Mortimer, A. J. *see* El Mikatti, N., (*ARS*) 529–530P
Morton, C. P. J., Armstrong, P. J. and McClure, J. H. Continuous subarachnoid infusion of local anaesthetic, (*ARS*) 533P
Morton, N. S. *see* Berry, C. B., (*C*) 332; Laycock, G. J. A. 356–362
Moseley, H. *see* Shankar, K. B., (*C*) 542–543
Muir, A. D., Reeder, M. K., Sear, J. W. and Foëx, P. Preoperative silent ischaemia is related to hypertension, (*ARS*) 540P
Mulas, M. *see* De Riu, P. L. 177–181
Munglani, R. *see* Sapsford, D. J., (*ARS*) 538P
Murayama, T., Shingu, K., Ogawa, T., Tomoda, K., Shindo, K., Tamai, S. and Mori, K. Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats 61–64
Murphy, F. L. *see* Longnecker, D. E., (*R*) 231
Murphy, P. G., Atkinson, R., Columb, M. O., Myers, D. S. and Day, P. Effect of propofol and thiopentone on free radical-induced haemolysis, (*ARS*) 532–533P
Murphy, P. G. *see* Columb, M. O., (*ARS*) 211P; Myers, D. S., (*ARS*) 222P
Murphy, P. J. *see* Barker, P. 314–315; Erskine, R. J., (*ARS*) 538–539P; Rabey, P. G. 346–348
Murray, J. M. and Trinick, T. R. Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol 643–644
Myers, D. S., Murphy, P. G., Majors, K. and Jones, J. G. Plasma antioxidant activity in stored blood, (*ARS*) 222P
Myers, D. S. *see* Murphy, P. G., (*ARS*) 532–533P

Nakajima, R. *see* Katoh, T. 259–262
Nebauer, A. E., Doenicke, A., Hoernecke, R., Angster, R. and Mayer, M. Does etomidate cause haemolysis? 58–60
Nevin, M. *see* Kaneko, K., (*ARS*) 537P; Matta, B., (*ARS*) 215P
Newton, D. E. F., Thornton, C., Konieczko, K. M., Jordan, C., Webster, N. R., Luff, N. P., Frith, C. D. and Doré, C. J. Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane 122–129
Ngan Kee, W. D. Steroid therapy and extradural analgesia, (*C*) 423
Ngan Kee, W. D., Jones, M. R., Thomas, P. and Worth, R. J. Extradural abscess complicating extradural anaesthesia for Caesarean section 647–652
Nielsen, M. *see* Williams, N. J., (*C*) 228
Nimmo, A. F., Wildsmith, J. A. W. and Drummond, G. B. Use of nasal oxygen cannulae to monitor postoperative breathing, (*ARS*) 539–540P
Nishikawa, T. Verapamil and cardiovascular responses to tracheal intubation, (*C*) 225
Nissen, I., Jensen, K. A. and Öhrström, J. K. Indomethacin in the management of postoperative pain 304–306
Noble, D. W. *see* Imray, I. McG., (*C*) 543–544
Nolan, K. M., Baxter, M. K., Winyard, J. A., Roulson, C. J. and Goldhill, D. R. Video surveillance of oxygen administration by mask in postoperative patients 194–196
Nolan, K. M., Winyard, J. A. and Goldhill, D. R. Comparison of nasal cannula and face mask for oxygen administration in postoperative patients, (*ARS*) 214–215P
Norén, H. *see* Wennberg, E. 13–18
Norman, J. One-compartment kinetics 387–396
Norman, J. *see* Saddler, J. M. 26–28
Norman, R. I. *see* Griffiths, R., (*ARS*) 530P
Norton, M. L. *see* Brown, A. C. D., (*R*) 231
Notcutt, W. G., Knowles, P. and Kaldas, R. Overdose of opioid from patient-controlled analgesia pumps 95–97
Nunn, J. F. *see* Matson, A. M., (*ARS*) 528–529P

O'Donnell, N. G., McSharry, C. P., Wilkinson, P. C. and Asbury, A. J. Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin 70–74
Ogawa, T. *see* Murayama, T. 61–64
Oh, T. E. *see* Bhatt, S. B. 298–303
Oh, T. H. *see* Bell, C., (*R*) 230
Öhrström, J. K. *see* Nissen, I. 304–306
O'Kelly, S. W. and Lawes, E. G. Bleeding time, (*C*) 330–331
Olsen, K. S., Henriksen, L., Dige-Petersen, H., Chraemmer-Jørgensen, B. and Rosenørn, J. Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam–fentanyl or isoflurane anaesthesia 263–268
Olsfanger, D. *see* Jedeikin, R. 349–351
Olukoga, A. O. *see* Vohra, A., (*ARS*) 212–213P
Ooi, R., Pattison, J. and Soni, N. Parallel Lack breathing system: fresh gas flow requirements during spontaneous ventilation, (*ARS*) 216P
Ooi, R. *see* Campkin, N., (*ARS*) 538P; Soni, N., (*ARS*) 215–216P
Orlikowski, C. E. P., Payne, A. J., Moodley, J. and Rocke, D. A. Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects 159–161
Oshima, T., Toyooka, H. and Amaha, K. Sternocleidomastoid muscle contractility at different levels of isoflurane anaesthesia in humans 236–239
Ostheimer, G. W., (editor) *Manual of Obstetric Anesthesia*, 2nd Edn, (*R*) 547–548
Ostheimer, G. W. *see* Miller, R. D., (*R*) 113
O'Toole, D. P. *see* Flynn, N. M., (*ARS*) 210P
Otteni, J. C. *see* Lleu, J. C., (*C*) 542
Oxorn, D. C., Whatley, G. S., Knox, J. W. D. and Hooper, J. The importance of activity and pretreatment in the prevention of suxamethonium myalgias 200–201

Page, R. *see* Ryan, T. 101–104
Page, R. J. *see* Shutt, L. E. 589–594
Palazzo, M. G. A., Ackers, J. W. L. and Evans, R. D. A logistic regression model for risk stratification of fixed patient factors for postoperative emesis, (*ARS*) 530P
Palmer, S. *see* Williams, N. J., (*C*) 228
Park, G. and Fulton, B. *The Management of Acute Pain*, (*R*) 548
Park, G. R. *see* Donaldson, M. D. J. 621–630; Kapadia, F. 640–642
Parker, C. J. R. and Hunter, J. M. Relationship of the train-of-four ratio to plasma atracurium concentration 274–280
Parker, C. J. R., Hunter, J. M. and Snowdon, S. L. Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium 439–443
Parker, C. J. R. *see* Devlin, J. C., (*ARS*) 217–218P; (*ARS*) 534–535P
Patel, M. and Swami, A. Spinal anaesthesia for Caesarean section, (*C*) 662
Patel, N., (editor) *Maternal Mortality—The Way Forward. Some Implications of the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–87*, (*R*) 547
Paton, R. D. *see* Laycock, G. J. A. 356–362
Patrick, J. A. *see* Kinsella, J. 19–22
Patterson, C. C. *see* McClune, S. 240–245
Pattison, J. *see* Ooi, R., (*ARS*) 216P; Soni, N., (*ARS*) 215–216P
Payne, A. J. *see* Orlikowski, C. E. P. 159–161
Peacock, J. E., Spiers, S. P. W., McLauchlan, G. A., Edmondson, W. C., Berthoud, M. and Reilly, C. S. Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients 363–367
Pereira, N. *see* Wilson, A., (*C*) 425
Persaud, S. J. *see* Desborough, J. P., (*ARS*) 532P
Peskett, M. J. Training in fibreoptic intubation, (*C*) 331
Peskett, M. J. *see* Merry, A. F. 92–94
Peter, K. *see* Mayer, M. 511–512; Welte, M. 637–639
Petruzzi, V. *see* De Riu, P. L. 177–181
Pettersen, B., Kongsgaard, U. and Aune, H. Skin injury in an infant with pulse oximetry 204–205; Skin injury with a pulse oximeter, (*C*) 665
Philips, B. J., Fergusson, S., Armstrong, P., Anderson, F. M. and Wildsmith, J. A. W. Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway 407–408
Phillips, A. S., McMurray, T. J. and Mirakhur, R. K. Comparison of propofol–fentanyl and isoflurane–fentanyl for maintenance of anaesthesia during cardiac surgery, (*ARS*) 211–212P

Phillips, B. J. *see* Devlin, J. C., (*ARS*) 217–218P
Pirogoff, N. and Fink, B. R. *Researches Practical and Physiological on Etherization*, (*R*) 333
Pitkänen, M. *see* Tuominen, M. 148–149; (*C*) 328–329
Plummer, J. L. *see* Short, T. G. 162–167
Pomfrett, C. J. D. *see* Wang, D. Y., (*ARS*) 221–222P
Ponte, J. *see* Bras, P., (*ARS*) 539P
Portenoy, R. K. *see* Max, M. B., (*R*) 230
Pottecher, T. *see* Lleu, J. C., (*C*) 542
Power, I. Bleeding time, (*C*) 329–330
Power, I., Cumming, A. D. and Pugh, G. C. Effect of diclofenac on renal function and prostacyclin generation after surgery 451–456
Prentice, J. W. *see* Kinsella, J. 19–22
Price, M. L., Millar, B., Grounds, M. and Cashman, J. Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate 172–176
Prior, C. *see* Tian, L. 284–287
Prithvi Raj, P., (editor) *Clinical Practice of Regional Anesthesia*, (*R*) 546–547
Prosser, A. *see* Shutt, L. E. 589–594
Prys-Roberts, C. *see* Browne, B. L. 570–576; Kaneko, K., (*ARS*) 537P; Mather, C. 40–44
Pugh, G. C. *see* Power, I. 451–456
Purday, J. P. and Towey, R. M. Apparent pacemaker failure caused by activation of ventricular threshold test by a magnetic instrument mat during general anaesthesia 645–646
Puri, G. D. and Singh, H. Bedside respiratory measurements with the Siemens–Elema CO_2 Analyzer, (*C*) 227; Ventilatory effects of laparoscopy under general anaesthesia, (*C*) 543
Putensen, C., Lingnau, W., Putensen-Himmer, G. and Herold, M. Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure 513–516
Putensen-Himmer, G. *see* Putensen, C. 513–516
Puttick, R. M., Diedericks, J., Sear, J. W., Glen, J. B., Foëx, P. and Ryder, W. A. Effect of graded infusion rates of propofol on regional and global left ventricular function in the dog 375–381

Quera, M.-A. *see* Beydon, L. 137–142

Rabey, P. G., Murphy, P. J., Langton, J. A., Barker, P. and Rowbotham, D. J. Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia 346–348
Rabey, P. G. and Smith, G. Anaesthetic factors contributing to postoperative nausea and vomiting 40–45S
Raftery, S. *see* Mather, C. 40–44
Ralston, S. J. and Head-Rapson, A. G. Application of EMLA before extradural insertion in labour, (*ARS*) 220–221P
Ramayya, G. P. *see* Ronald, A. L. 105–107
Räsänen, J. *see* Grenvik, A., (*R*) 334
Rauss, A. *see* Beydon, L. 137–142
Read, M. S. Insulated regional block needles, (*C*) 423
Rebiere, T. *see* Cohendy, R. 595–598
Reckendorfer, H., Burgmann, H., Sperlich, M., Tüchy, G. L., Feigl, W., Spieckermann, P. G., Weindlmayr-Göttel, M. and Schwarz, S. Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver 288–291
Reddy, T. R. *see* Mettam, I. M. 420–421
Redman, C. W. G. *see* de Swiet, M., (*C*) 109
Reeder, M. K. *see* Muir, A. D., (*ARS*) 540P
Rees, G. A. D. *see* Crosby, D. L., (*R*) 426–427
Rehder, K. *see* Hatch, D. J., (*ARS*) 217P
Reid, T. M. S. *see* Imray, I. McG., (*C*) 543–544
Reilly, C. S. *see* McFie, A. G. 447–450; Magides, A. D., (*ARS*) 529P; Michael, S. 577–579; Peacock, J. E. 363–367
Reinsel, R. A. *see* Veselis, R. A. 246–254
Reinstrup, P., Uski, T. and Messeter, K. Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin $F_{2\alpha}$ in isolated human pial arteries 615–620
Reynolds, F. *see* Carson, R. J. 150–153
Rice, A. S. C. and McMahon, S. B. Peripheral nerve injury caused by injection needles used in regional anaesthesia: influence of bevel configuration, studied in a rat model 433–438
Rifat, K. *see* Dottrens, M. 9–12
Rigor, B. M. *see* Andrews, P. J. D. 401–403
Robertson, E. N. *see* Hull, J. M., (*ARS*) 534P
Robinson, B. J. and Robinson, G. M. Alcohol withdrawal treatment with clonidine, (*C*) 328
Robinson, G. M. *see* Robinson, B. J., (*C*) 328
Rocke, D. A. *see* Orlikowski, C. E. P. 159–161
Roizen, M. F. *see* Miller, R. D., (*R*) 113
Ronald, A. L., Ramayya, G. P. and Chambers, W. A. Continuous collection of pulse oximetry data: a new, inexpensive, portable computerized method 105–107
Rosenberg, P. H. *see* Tuominen, M. 148–149; (*C*) 328–329
Rosenørn, J. *see* Olsen, K. S. 263–268
Roulson, C. J. *see* Nolan, K. M. 194–196
Rowbotham, D. J. Current management of postoperative nausea and vomiting 46–59S
Rowbotham, D. J. and Smith, G. Introduction 1S
Rowbotham, D. J. *see* Atcheson, R., (*ARS*) 531P; Barker, P. 314–315; Griffiths, R., (*ARS*) 530P; Rabey, P. G. 346–348; Trotter, T. N. 352–355
Royston, B. D. *see* Matson, A. M., (*ARS*) 528–529P
Ruiz, K. *see* Keenan, G. M. A., (*ARS*) 533P
Runciman, W. B. *see* Huang, Y. F. 368–374
Russ, W. *see* Boldt, J. 45–50
Russell, D. and Kenny, G. N. C. 5-HT_3 antagonists and postoperative nausea and vomiting 63–68S
Russell, I. F. and Vucevic, M. Spinal anaesthesia for Caesarean section, (*C*) 662
Rutten, A. J. *see* Huang, Y. F. 368–374
Ryall, D. *see* Blumgart, C. H. 457–460
Ryan, T., Page, R., Bouchier-Hayes, D. and Cunningham, A. J. Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: comparison with the thermodilution technique 101–104
Ryder, W. A. *see* Puttick, R. M. 375–381

Saddler, J. M., Marks, L. F. and Norman, J. Comparison of atracurium-induced neuromuscular block in rectus abdominis and hand muscles of man 26–28
van Saene, H. K. F. *see* Stoutenbeek, C. P., (*R*) 112–113
Samara, B. *see* Cook, D. R. 580–585
Samsoon, G., Wood, M. E., Knight-George, A. B. and Britt, R. P. General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients 653–656
Sandler, A. N. *see* Katz, J., (*C*) 424
Sandmann, W. *see* Stühmeier, K. D. 602–606
Sapsford, D. J. and Jones, J. G. Derivation of $\dot{V}/\dot{Q}$ from the position of the $P_{I_{O_2}}$ *vs* $S_{p_{O_2}}$ curve, (*ARS*) 541P
Sapsford, D. J., Munglani, R. and Jones, J. G. Coherence in the auditory evoked response as a measure of arousal during anaesthesia, (*ARS*) 538P
Sarihasan, B. *see* Esener, Z. 586–588
Sato, S. *see* Koga, Y. 65–69
Saul, C. *see* Hatch, D. J., (*ARS*) 217P
Schrader, M. Inspiratory to end-tidal oxygen difference, (*C*) 663
Schwarz, S. *see* Reckendorfer, H. 288–291
Scott, D. H. T. *see* Armstrong, P. J., (*ARS*) 533–534P
Scott, P. V. and Fischer, H. B. J. Intrathecal diamorphine–bupivacaine during labour, (*C*) 108
Scott, R. P. F. Atracurium and histamine, (*C*) 110
Scott, R. P. F. *see* Gill, R. S. 444–446
Scriven, M. W., Burgess, N. A., Woodsford, P. W. and Lewis, M. H. Delayed septicaemia after extradural steroid treatment, (*C*) 422–423
Seaman, M. J. *see* Donaldson, M. D. J. 621–630
Sear, J. W. *see* Howell, S., (*ARS*) 536P; Muir, A. D., (*ARS*) 540P; Puttick, R. M. 375–381
Sedgwick, J. *see* Charlton, G. A. 206–209
Seeberger, M. D. and Urwyler, A. Lumbovertebral syndrome after extradural blood patch 414–416
Seymour, D. G. *see* Crosby, D. L., (*R*) 426–427
Shachor, D. *see* Jedeikin, R. 349–351
Shah, M. V. *see* Bennett, M. W. R., (*ARS*) 220P; Columb, M. O., (*ARS*) 211P; Keenan, G. M. A., (*ARS*) 533P
Shale, D. J. *see* Williams, W. R. 508–510
Shankar, K. B., Kumar, A. Y. and Moseley, H. Ventilatory effects of laparoscopy under general anaesthesia, (*C*) 542–543
Shantha, T. R. Retrograde intubation using the subcricoid region, (*C*) 542
Sharples, L. D. *see* Bethune, D. W. 197–199
Shelly, M. P. *see* Kapadia, F. 640–642
Shepherd, D. *see* Wheatley, R. G. 558–561
Shepstone, B. J. *see* Sykes, M. K., (*R*) 666
Shindo, K. *see* Murayama, T. 61–64
Shingu, K. *see* Murayama, T. 61–64

Short, T. G., Plummer, J. L. and Chui, P. T. Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil 162–167
Shutt, L. E., Valentine, S. J., Wee, W. Y. K., Page, R. J., Prosser, A. and Thomas, T. A. Spinal anaesthesia for Caesarean section: comparison of 22-gauge and 25-gauge Whiteacre needles with 26-gauge Quincke needles 589–594
Simon, E. *see* Dodd, F. M., (*ARS*) 526–527P
Simpson, P. Perioperative blood loss and its reduction: the role of the anaesthetist 498–507
Singh, H. *see* Puri, G. D., (*C*) 227; (*C*) 543
Sissons, G. R. *see* McMenemin, I. M. 417–419
Smith, D. C. Effects of skin blood flow and temperature on skin–electrode impedance and offset potential, (*ARS*) 223P; Recording electrode impedance has no effect on evoked EMG responses, (*ARS*) 535–536P
Smith, D. C. and Booth, J. V. Influence of temperature and posture changes on evoked electromyography, (*ARS*) 223P
Smith, G. Dual publication of abstracts, (*C*) 227
Smith, G. *see* Barker, P. 23–25; Erskine, R. J., (*ARS*) 538–539P; Fell, D., (*R*) 667–668; Langton, J., (*C*) 661–662; Rabey, P. G. 40–45S; Rowbotham, D. J. 1S
Smith, R. *see* Grenvik, A., (*R*) 334
Sneyd, J. R. *see* Wang, D. Y., (*ARS*) 221–222P
Sneyd, R. *see* Lewis, I. H., (*C*) 329
Snowdon, S. L. *see* Parker, C. J. R. 439–443
Sodeyama, N. *see* Koga, Y. 65–69
Sold, M. *see* Engelhardt, W. 75–80
Sommerville, D. *see* Entwistle, M. D., (*ARS*) 536–537P
Soni, N., Ooi, R. and Pattison, J. Rebreathing in the Magill breathing system, (*ARS*) 215–216P
Soni, N. *see* Campkin, N., (*ARS*) 538P; Ooi, R., (*ARS*) 216P
Sonntag, H. *see* Lange, H. 478–481; Stephan, H. 51–57
Spencer, G.E. *see* Hopkins, P. M., (*ARS*) 210–211P
Sperlich, M. *see* Reckendorfer, H. 288–291
Spieckermann, P. G. *see* Reckendorfer, H. 288–291
Spiers, S. P. W. *see* Peacock, J. E. 363–367
Spiss, C. K. *see* Werba, A. 382–386
Spurrier, E. A. *see* Tobin, J. R. 482–486
Stanley, J. C. *see* McCarthy, G. J. 281–283
Stanley, K. P. *see* Magides, A. D., (*ARS*) 529P
Stein, C. *see* Welte, M. 637–639
Steinbereithner, K. *see* Werba, A. 382–386
Stenqvist, O. *see* Bengtson, J. P., (*C*) 663
Stephan, H., Weyland, A., Kazmaier, S., Henze, T., Menck, S. and Sonntag, H. Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome 51–57
Stephan, H. *see* Lange, H. 478–481
Stephen, J. P. H. *see* Hicks, R. G. 130–136
Stewart, A. D. *see* Ball, S. P., (*ARS*) 222–223P
Stiller, R. L. *see* Cook, D. R. 580–585
Stoelting, R. K. *see* Miller, R. D., (*R*) 113
Stoutenbeek, C. P. and van Saene, H. K. F., (editors) *Infection and the Anaesthetist*, (*R*) 112–113
Stühmeier, K. D., Mainzer, B., Sandmann, W. and Tarnow, J. Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery 602–606
Suguro, Y. *see* Katoh, T. 259–262
Sunder-Plassmann, L. *see* Welte, M. 637–639
Suter, P. M. *see* Artigas, A., (*R*) 427
Sutton, D. N. *see* Charlton, G. A. 206–209
Swami, A. *see* Patel, M., (*C*) 662
Swanson, P. W. *see* Lee, M. G. 522–525
Sweeney, B. P. *see* Williams, A. R., (*ARS*) 216–217P
de Swiet, M. and Redman, C. W. G. Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), (*C*) 109
Sykes, M. K., Vickers, M. D., Hull, C. J., Winterburn, P. J. and Shepstone, B. J. *Principles of Measurement and Monitoring in Anaesthesia and Intensive Care*, 3rd Edn, (*R*) 666

Taivainen, T. *see* Tuominen, M., (*C*) 328–329
Takahashi, M. *see* Koga, Y. 65–69
Tam, Y. K. *see* Finegan, B. A. 492–497
Tamai, S. *see* Murayama, T. 61–64
Tansey, P. *see* Haynes, S. R. 599–601
Tarnow, J. *see* Stühmeier, K. D. 602–606
Taylor, H. *see* Gataure, P. S. 657–658
Taylor, I. N., Kenny, G. N. C. and Glen, J. B. Pharmacodynamic stability of a mixture of propofol and alfentanil 168–171
Taylor, T. H. and Goldhill, D. R. *Standards of Care in Anaesthesia*, (*R*) 334
Tehan, B. Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine 520–521
Testa, C. *see* De Riu, P. L. 177–181
Thomas, A. N., Bergesio, R., Hyatt, J. and Barker, S. J. Mouth mask ventilation: use of a Pall Ultipor breathing system and effect of mask design, (*ARS*) 527–528P
Thomas, A. N., Dang, P. T., Hyatt, J. and Trinh, T. N. A new technique for two-hand bag valve mask ventilation 397–398
Thomas, P. *see* Ngan Kee, W. D. 647–652
Thomas, T. A. *see* Shutt, L. E. 589–594
Thompson-Hill, L. M. *see* Blumgart, C. H. 457–460
Thornton, C. *see* Newton, D. E. F. 122–129
Tian, L., Mehta, M. P., Prior, C. and Marshall, I. G. Relative pre- and postjunctional effects of a new vecuronium analogue, Org 9426, at the rat neuromuscular junction 284–287
Tobin, J. R., Spurrier, E. A. and Wetzel, R. C. Anaesthesia for critically ill children during magnetic resonance imaging 482–486
Tobin, M. J., (editor) *Respiratory Monitoring* (*Contemporary Management in Critical Care* series), (*R*) 666
Todd, J. G. *see* Chaudhri, S. 607–610
Toff, N. J. Use of a dental mirror in simulated difficult laryngoscopy, (*ARS*) 218–219P
Tolley, P. M., Watts, A. D. J. and Hickman, J. A. Comparison of the use of the laryngeal mask and face mask by inexperienced personnel 320–321
Tomlinson, B. *see* Bhatt, S. B. 298–303
Tomoda, K. *see* Murayama, T. 61–64
Tong, W. P. *see* Veselis, R. A. 246–254
Towey, R. M. *see* Purday, J. P. 645–646
Toyooka, H. *see* Oshima, T. 236–239
Tramer, M. *see* Wilder-Smith, O. H. G., (*C*) 663–664
Trinh, T. N. *see* Thomas, A. N. 397–398
Trinick, T. R. *see* Murray, J. M. 643–644
Trotter, T. N., Langton, J. A., Barker, P. and Rowbotham, D. J. Perioperative continuous monitoring of ST-segment changes in patients undergoing elective Caesarean section 352–355
Tsai, S. K., Lee, C., Kwan, W.-F. and Chen, B.-J. Recovery of cognitive functions after anaesthesia with desflurane or isoflurane and nitrous oxide 255–258
Tüchy, G. L. *see* Reckendorfer, H. 288–291
Tuominen, M., Pitkänen, M. and Rosenberg, P. H. Effect of speed of injection of 0.5% plain bupivacaine on the spread of spinal anaesthesia 148–149
Tuominen, M., Pitkanen, M., Taivainen, T. and Rosenberg, P. H. Spread of spinal anaesthesia, (*C*) 328–329
Tyers, M. B. *see* Bunce, K. T. 60–62S

Upton, R. N. *see* Huang, Y. F. 368–374
Urban, B. W. *see* Frenkel, C. 292–297
Urwyler, A. *see* Seeberger, M. D. 414–416
Uski, T. *see* Reinstrup, P. 615–620
Üstün, E. *see* Esener, Z. 586–588
Utting, J. E. The era of relaxant anaesthesia, (*E*) 551–553

Valentine, S. J. *see* Shutt, L. E. 589–594
Vanlinthout, L. E. H., van Egmond, J., de Boo, T., Lerou, J. G. C., Wevers, R. A. and Booij, L. H. D. J. Factors affecting magnitude and time course of neuromuscular block produced by suxamethonium 29–35
Varley, S. *see* Cook, L. B. 322–324.
Vaughan, R. S. *see* Cobley, M., (*C*) 225
Vegfors, M. *see* Gupta, A., (*C*) 422
Verbeek, A. M. *see* Hull, J. M., (*ARS*) 534P
Verbessem, D. *see* Verborgh, C. 36–39
Verborgh, C., Verbessem, D. and Camu, F. Haemodynamic effects of isoflurane during propofol anaesthesia 36–39
Vergnaud, M.-C. *see* Laroche, D. 611–614
Veroli, P. and Benhamou, D. Comparison of hypertonic saline (5%), isotonic saline and Ringer's lactate solutions for fluid preloading before lumbar extradural anaesthesia 461–464
Veselis, R. A., Reinsel, R. A., Wroński, M., Marino, P., Tong, W. P. and Bedford, R. F. EEG and memory effects of low-dose infusions of propofol 246–254
Vickers, M. D. *see* Sykes, M. K., (*R*) 666
Vohra, A., Kumar, S., Charlton, A. J., Olukoga, A. O., McLeod, D. and Boulton, A. J. M. Effect of diabetic autonomic dysfunction on the cardiovascular responses to induction of anaesthesia and tracheal intubation, (*ARS*) 212–213P
Vucevic, M. *see* Russell, I. F., (*C*) 662

Walker, I. A. *see* Bethune, D. W. 197–199

Wang, C. Y. Respiratory depression after extradural fentanyl, (*C*) 544

Wang, D. Y., Sneyd, J. R., Pomfrett, C. J. D. and Healy, T. E. J. Effect of physiotherapy on EEG spectral derivatives in sedated patients in the intensive care unit, (*ARS*) 221–222P

Wanigasekera, V. *see* Howell, S., (*ARS*) 536P

Ward, M. E. A new look at the breath of life, (*E*) 339–340

Wardall, G. J. *see* Merry, A. F. 92–94

Watts, A. D. J. *see* Tolley, P. M. 320–321

Webster, N. R. *see* Newton, D. E. F. 122–129

Wee, M. Y. K., Geeurickx, A. and Wimalaratna, S. A method to facilitate regional anaesthesia by detection of mixed nerve action potentials 411–413

Wee, W. Y. K. *see* Shutt, L. E. 589–594

Weindlmayr-Goettel, M. *see* Werba, A. 382–386

Weindlmayr-Göttel, M. *see* Reckendorfer, H. 288–291

Welch, R. M. *see* Cook, D. R. 580–585

Welte, M., Haimerl, E., Groh, J., Briegel, J., Sunder-Plassmann, L., Herz, A., Peter, K. and Stein, C. Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy 637–639

Wennberg, E., Frid, I., Haljamäe, H. and Norén, H. Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section 13–18

Werba, A., Gilly, H., Weindlmayr-Goettel, M., Spiss, C. K., Steinbereithner, K., Czech, T. and Agoston, S. Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood–brain barrier 382–386

Wetchler, B. V. Postoperative nausea and vomiting in day-case surgery 33–39S

Wetzel, R. C. *see* Tobin, J. R. 482–486

Wevers, R. A. *see* Vanlinthout, L. E. H. 29–35

Weyland, A. *see* Stephan, H. 51–57

Whatley, G. S. *see* Oxorn, D. C. 200–201

Wheatley, R. G., Shepherd, D., Jackson, I. J. B., Madej, T. H. and Hunter, D. Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia 558–561

Wheatley, R. G. *see* Madej, T. H. 554–557

White, D. C. *see* McHale, S. P., (*ARS*) 529P; Matson, A. M., (*ARS*) 528–529P; Wolff, A. H., (*ARS*) 539P

White, P. F., (editor) *Kinetics of Anaesthetic Drugs in Clinical Anesthesiology*, (*R*) 667

Whiting, R. W. *see* Finegan, B. A. 492–497

Wild, C. J. *see* Merry, A. F. 92–94

Wilder-Smith, C. H. Bacterial overgrowth and gastric dysfunction, (*C*) 545

Wilder-Smith, O. H. G., Borgeat, A., Tramer, M. and Morel, D. R. Pre-emptive extradural analgesia, (*C*) 663–664

Wildsmith, J. A. W. *see* Nimmo, A. F., (*ARS*) 539–540P; Philips, B. J. 407–408

Wilkinson, P. C. *see* O'Donnell, N. G. 70–74

Willard, T. B. and Beatty, P. C. W. Effect of speed of response of capnographs on the accuracy of measurements during anaesthesia, (*ARS*) 213P

Williams, A. R. Damage to coaxial breathing systems, (*C*) 425

Williams, A. R. and Sweeney, B. P. Incidence and severity of postoperative nausea and vomiting in patients exposed to positive intraoperative suggestions, (*ARS*) 216–217P

Williams, N. J., Grimes, A., Palmer, S. and Nielsen, M. Oxygen wastage by oxygen–air mixers, (*C*) 228

Williams, W. R. and Shale, D. J. *In vitro* displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs 508–510

Wilson, A. and Pereira, N. Unnecessary preoperative investigations in children, (*C*) 425

Wilson, I. *see* Langton, J., (*C*) 661–662

Wilson, I. G. *see* Barker, P. 23–25

Wilson, L. E. *see* Hatch, D. J., (*ARS*) 217P

Wimalaratna, S. *see* Wee, M. Y. K. 411–413

Winlow, W. and Yar, T. Effects of halothane on cultured neurones, (*ARS*) 530–531P

Winlow, W. *see* Hopkins, P. M., (*ARS*) 210–211P

Winterburn, P. J. *see* Sykes, M. K., (*R*) 666

Winyard, J. A. *see* Nolan, K. M. 194–196; (*ARS*) 214–215P

Wittmann, F. W. *see* Wittmann, P. H., (*C*) 332

Wittmann, P. H. and Wittmann, F. W. Blood loss during total hip replacement, (*C*) 332

Wolf, A. R. *see* Browne, B. L. 570–576

Wolff, A. H., McHale, S. P. and White, D. C. Describing circle systems, (*ARS*) 539P

Wood, M. E. *see* Samsoon, G. 653–656

Wood, P. *see* Ip Yam, C., (*C*) 111

Wood, P. R., Dresner, M. and Lawler, P. G. P. Training in fibreoptic tracheal intubation in the North of England 202–203

Woodforth, I. J. *see* Hicks, R. G. 130–136

Woodsford, P. W. *see* Scriven, M. W., (*C*) 422–423

Worth, R. J. *see* Ngan Kee, W. D. 647–652

Wright, P. M. C. and George, K. A. Extradural fentanyl–bupivacaine compared with patient controlled analgesia using i.v. morphine after upper abdominal surgery, (*ARS*) 219–220P

Wright, P. M. C. *see* McClune, S. 240–245

Wroński, M. *see* Veselis, R. A. 246–254

Yaddanapudi, L. N., Kashyap, L. and Mallick, A. Hypoxaemia and insertion of the laryngeal mask airway, (*C*) 661

Yaku, H. and Mikawa, K. Verapamil and cardiovascular responses to tracheal intubation, (*C*) 225–226

Yar, T. *see* Hopkins, P. M., (*ARS*) 210–211P; Winlow, W., (*ARS*) 530–531P

Young, H. *see* Eddleston, J. M. 154–158

Young, L. E., Long, K. J., Darke, P. G. G. and Jones, R. S. Effects of detomidine, dopamine and dobutamine on selected Doppler echocardiographic variables in the horse, (*ARS*) 222P

Zaloga, G. P. *The Critical Care Drug Handbook*, (*R*) 548

Zander, R. and Mertzlufft, F., (editors) *The Oxygen Status of Arterial Blood*, (*R*) 333

Zapol, W. M. *see* Artigas, A., (*R*) 427

Zbinden, A. M. European Standardization Committee on Anaesthetic Equipment, (*C*) 543

Zickmann, B. *see* Boldt, J. 45–50

Ziehlmann, S. *see* Lange, H. 478–481

SUBJECT INDEX

Acid–base equilibrium, Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome, Stephan, H., *et al.* 51–57

Acid–base equilibrium, pH, Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section, Wennberg, E., *et al.* 13–18

——, Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin $F_{2\alpha}$ in isolated human pial arteries, Reinstrup, P., *et al.* 615–620

Adductor pollicis, Factors affecting magnitude and time course of neuromuscular block produced by suxamethonium, Vanlinthout, L. E. H., *et al.* 29–35

——, Influence of circulating drug on recovery of neuromuscular block in the isolated forearm, Hood, J. R., *et al.*, (*ARS*) 535P

Adult Respiratory Distress Syndrome, Artigas, A., *et al.*, (editors), (*R*) 427

Advances in Pain Research and Therapy, Volume 18: The Design of Analgesic Clinical Trials, Max, M. B., *et al.*, (editors), (*R*) 230

Age factors, Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly, McCarthy, G. J., *et al.* 281–283

——, Effect of age on the sensitivity of upper airway reflexes, Erskine, R. J., *et al.*, (*ARS*) 538–539P

——, Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium, Parker, C. J. R., *et al.* 439–443

——, Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients, Peacock, J. E., *et al.* 363–367

——, Postoperative oxygenation in the elderly after ophthalmic surgery: comparison of local and general anaesthesia, McCarthy, G., *et al.*, (*ARS*) 213–214P

——, The National Confidential Enquiry into Perioperative Deaths 1990, Graham, S. G., (*E*) 431–432

Airway, A new look at the breath of life, Ward, M. E., (*E*) 339–340

——, Advances in cardiopulmonary resuscitation, Baskett, P. J. F. 182–193

Airway, obstruction, Life-threatening acute respiratory distress in late pregnancy, Mettam, I. M., *et al.* 420–421

Airway, patency, Effect of a cervical collar on the tidal volume of anaesthetized adult patients, Dodd, F. M., *et al.*, (*ARS*) 526–527P

Airway, pressure, Auto-PEEP, lung volume and sternotomy, Fletcher, R., (*ARS*) 527P

Airway, reflexes, Effect of a cervical collar on the tidal volume of anaesthetized adult patients, Dodd, F. M., *et al.*, (*ARS*) 526–527P

——, Effect of age on the sensitivity of upper airway reflexes, Erskine, R. J., *et al.*, (*ARS*) 538–539P

——, Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol, Barker, P., *et al.* 23–25

——, Vocal cord movement on induction of anaesthesia, Fink, B. R., (*C*) 661

——, Vocal cord movement on induction of anaesthesia, Langton, J., *et al.*, (*C*) 661–662

Alcohol, withdrawal, Alcohol withdrawal treatment with clonidine, Robinson, B. J., *et al.*, (*C*) 328

Allergy, Anaphylactoid or carcinoid? Batchelor, A. M., *et al.* 325–327

——, Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs, Laroche, D., *et al.* 611–614

——, *In vitro* displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs, Williams, W. R., *et al.* 508–510

——, Radioimmunoassay tests and anaphylaxis, Imray, I. McG., *et al.*, (*C*) 543–544

Anaesthesia, audit, The National Confidential Enquiry into Perioperative Deaths 1990, Graham, S. G., (*E*) 431–432

Anaesthesia, day-case, Four anaesthetic techniques for day-case oral surgery, Martlew, R., *et al.*, (*ARS*) 219P

Anaesthesia, depth, Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane, Newton, D. E. F., *et al.* 122–129

——, Coherence in the auditory evoked response as a measure of arousal during anaesthesia, Sapsford, D. J., *et al.*, (*ARS*) 538P

——, Effect of physiotherapy on EEG spectral derivatives in sedated patients in the intensive care unit, Wang, D. Y., *et al.*, (*ARS*) 221–222P

Anaesthesia, duration, Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol, Murray, J. M., *et al.* 643–644

Anaesthesia for Ophthalmic and Otolaryngologic Surgery, McGoldrick, E., (editor), (*R*) 667

Anaesthesia, general, Effect of fentanyl on ventilatory resistances during barbiturate general anaesthesia, Cohendy, R., *et al.* 595–598

——, Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia, Rabey, P. G., *et al.* 346–348

——, General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients, Samsoon, G., *et al.* 653–656

——, Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion, Bethune, D. W., *et al.* 197–199

——, Postoperative oxygenation in the elderly after ophthalmic surgery: comparison of local and general anaesthesia, McCarthy, G., *et al.*, (*ARS*) 213–214P

——, Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, Barker, P., *et al.* 314–315

Anaesthesia, geriatric, Effect of age on the sensitivity of upper airway reflexes, Erskine, R. J., *et al.*, (*ARS*) 538–539P

——, Postoperative oxygenation in the elderly after ophthalmic surgery: comparison of local and general anaesthesia, McCarthy, G., *et al.*, (*ARS*) 213–214P

Anaesthesia, neurosurgical, Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam–fentanyl or isoflurane anaesthesia, Olsen, K. S., *et al.* 263–268

Anaesthesia, obstetric, Accidental subdural catheterization: radiological evidence of a possible mechanism for spinal cord damage, McMenemin, I. M., *et al.* 417–419

——, Anaesthesia for Caesarean section in a patient with Ehlers–Danlos syndrome type IV, Brighouse, D., *et al.* 517–519

——, Antenatal assessment for anaesthesia, Cody, M. W., *et al.*, (*C*) 332

——, Application of EMLA before extradural insertion in labour, Ralston, S. J., *et al.*, (*ARS*) 220–221P

——, Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section, Wennberg, E., *et al.* 13–18

——, Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia, Eddleston, J. M., *et al.* 154–158

——, Extradural abscess complicating extradural anaesthesia for Caesarean section, Ngan Kee, W. D., *et al.* 647–652

——, Influence of vitamin B_{12} status on the inactivation of methionine synthase by nitrous oxide, Landon, M. J., *et al.* 81–86

——, Intrathecal diamorphine–bupivacaine during labour, Kestin, I. G., (*C*) 108

——, Intrathecal diamorphine–bupivacaine during labour, Scott, P. V., *et al.*, (*C*) 108

——, Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic, Blumgart, C. H., *et al.* 457–460

——, Perioperative continuous monitoring of ST-segment changes in patients undergoing elective Caesarean section, Trotter, T. N., *et al.* 352–355

——, Spinal anaesthesia for Caesarean section, Patel, M., *et al.*, (*C*) 662
——, Spinal anaesthesia for Caesarean section, Russell, I. F., *et al.*, (*C*) 662
——, Spinal anaesthesia for Caesarean section: comparison of 22-gauge and 25-gauge Whiteacre needles with 26-gauge Quincke needles, Shutt, L. E., *et al.* 589–594
——, Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum, Esener, Z., *et al.* 586–588
——, Transient bradycardia associated with extradural blood patch after inadvertent dural puncture in parturients, Andrews, P. J. D., *et al.* 401–403
Anaesthesia, paediatric, Anaesthesia for critically ill children during magnetic resonance imaging, Tobin, J. R., *et al.* 482–486
——, Anaesthetic management of renin secreting nephroblastoma, Charlton, G. A., *et al.* 206–209
——, Effects of isoflurane anaesthesia on the median nerve somatosensory evoked potential in children, Mason, D. G., *et al.* 562–566
——, Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery, Michael, S., *et al.* 577–579
——, Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia, Browne, B. L., *et al.* 570–576
——, Sequential measurement of the median nerve somatosensory evoked potential during isoflurane anaesthesia in children, Mason, D. G., *et al.* 567–569
——, Venous sequelae of diclofenac, Berry, C. B., *et al.*, (*C*) 332
——, Venous sequelae of diclofenac, Gopinath, R., (*C*) 332
Anaesthetic–analgesic regimens, Comparison of propofol–fentanyl and isoflurane–fentanyl for maintenance of anaesthesia during cardiac surgery, Phillips, A. S., *et al.*, (*ARS*) 211–212P
——, Extradural fentanyl–bupivacaine compared with patient controlled analgesia using i.v. morphine after upper abdominal surgery, Wright, P. M. C., *et al.*, (*ARS*) 219–220P
——, Pharmacodynamic stability of a mixture of propofol and alfentanil, Taylor, I. N., *et al.* 168–171
——, Pre-emptive extradural analgesia, Dahl, J. B., *et al.*, (*C*) 664–665
——, Pre-emptive extradural analgesia, Wilder-Smith, O. H. G., *et al.*, (*C*) 663–664
Anaesthetic techniques, endobronchial, Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis, Jedeikin, R., *et al.* 349–351
Anaesthetic techniques, extradural, Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine, Tehan, B. 520–521
——, Accidental subdural catheterization: radiological evidence of a possible mechanism for spinal cord damage, McMenemin, I. M., *et al.* 417–419
——, Anaesthesia for Caesarean section in a patient with Ehlers–Danlos syndrome type IV, Brighouse, D., *et al.* 517–519
——, Application of EMLA before extradural insertion in labour, Ralston, S. J., *et al.*, (*ARS*) 220–221P
——, Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), Macdonald, R., (*C*) 109–110
——, Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), de Swiet, M., *et al.*, (*C*) 109
——, Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section, Wennberg, E., *et al.* 13–18
——, Comparison of extradural administration of sufentanil, morphine and sufentanil–morphine combination after Caesarean section, Dottrens, M., *et al.* 9–12
——, Comparison of hypertonic saline (5%), isotonic saline and Ringer's lactate solutions for fluid preloading before lumbar extradural anaesthesia, Veroli, P., *et al.* 461–464
——, Extradural abscess complicating extradural anaesthesia for Caesarean section, Ngan Kee, W. D., *et al.* 647–652
——, Extradural fentanyl–bupivacaine compared with patient controlled analgesia using i.v. morphine after upper abdominal surgery, Wright, P. M. C., *et al.*, (*ARS*) 219–220P
——, Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery, Dahl, J. B., *et al.* 4–8
——, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.* 414–416
——, Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic, Blumgart, C. H., *et al.* 457–460
——, Perioperative continuous monitoring of ST-segment changes in patients undergoing elective Caesarean section, Trotter, T. N., *et al.* 352–355
——, Respiratory depression after extradural fentanyl, Wang, C. Y., (*C*) 544
——, Transient bradycardia associated with extradural blood patch after inadvertent dural puncture in parturients, Andrews, P. J. D., *et al.* 401–403
Anaesthetic techniques, fibreoptic, Training in fibreoptic intubation, Peskett, M. J., (*C*) 331
——, Training in fibreoptic tracheal intubation in the North of England, Wood, P. R., *et al.* 202–203
Anaesthetic techniques, hypotensive, Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma, Chaudhri, S., *et al.* 607–610
——, Perioperative blood loss and its reduction: the role of the anaesthetist, Simpson, P. 498–507
Anaesthetic techniques, hypothermia, Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome, Stephan, H., *et al.* 51–57
Anaesthetic techniques, induction, Hypoxaemia and insertion of the laryngeal mask airway, Gillies, G. W. A., (*C*) 661
——, Hypoxaemia and insertion of the laryngeal mask airway, Yaddanapudi, L. N., *et al.*, (*C*) 661
——, Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients, Peacock, J. E., *et al.* 363–367
——, Synergistic interaction between midazolam and propofol, McClune, S., *et al.* 240–245
Anaesthetic techniques, inhalation, Four anaesthetic techniques for day-case oral surgery, Martlew, R., *et al.*, (*ARS*) 219P
——, Laryngeal mask airway: a more successful method of insertion, Matta, B., *et al.*, (*ARS*) 215P
Anaesthetic techniques, i.v. bolus, Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia, Eddleston, J. M., *et al.* 154–158
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects on circulatory function, Huang, Y. F., *et al.* 368–374
Anaesthetic techniques, i.v. infusion, Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia, Eddleston, J. M., *et al.* 154–158
——, Effect of graded infusion rates of propofol on regional and global left ventricular function in the dog, Puttick, R. M., *et al.* 375–381
——, Four anaesthetic techniques for day-case oral surgery, Martlew, R., *et al.*, (*ARS*) 219P
——, Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients, Peacock, J. E., *et al.* 363–367
——, Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion, Bethune, D. W., *et al.* 197–199
——, Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia, Browne, B. L., *et al.* 570–576
Anaesthetic techniques, loading dose, Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section, Wennberg, E., *et al.* 13–18
Anaesthetic techniques, regional, A method to facilitate regional anaesthesia by detection of mixed nerve action potentials, Wee, M. Y. K., *et al.* 411–413
——, Peripheral nerve damage and regional anaesthesia, Chambers, W. A., (*E*) 429–430
——, Peripheral nerve injury caused by injection needles used in regional anaesthesia: influence of bevel configuration, studied in a rat model, Rice, A. S. C., *et al.* 433–438
Anaesthetic techniques, regional, interpleural, Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy, Welte, M., *et al.* 637–639
Anaesthetic techniques, regional, palate, Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery, Michael, S., *et al.* 577–579
Anaesthetic techniques, regional, peribulbar, Postoperative oxygenation in the elderly after ophthalmic surgery: comparison of local and general anaesthesia, McCarthy, G., *et al.*, (*ARS*) 213–214P
Anaesthetic techniques, subarachnoid, A puncture

technique for continuous subarachnoid block, De Andrés, J. A., (*C*) 544–545
——, Anaesthesia for Caesarean section in a patient with Ehlers–Danlos syndrome type IV, Brighouse, D., *et al.* 517–519
——, Continuous subarachnoid infusion of local anaesthetic, Morton, C. P. J., *et al.*, (*ARS*) 533P
——, Effect of speed of injection of 0.5% plain bupivacaine on the spread of spinal anaesthesia, Tuominen, M., *et al.* 148–149
——, Intrathecal diamorphine–bupivacaine during labour, Kestin, I. G., (*C*) 108
——, Intrathecal diamorphine–bupivacaine during labour, Scott, P. V., *et al.*, (*C*) 108
——, Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic, Blumgart, C. H., *et al.* 457–460
——, Metallic fragments and the combined spinal–extradural technique, Carrie, L. E. S., (*C*) 662–663
——, Metallic fragments and the combined spinal–extradural technique, Eldor, J., (*C*) 663
——, Perioperative continuous monitoring of ST-segment changes in patients undergoing elective Caesarean section, Trotter, T. N., *et al.* 352–355
——, Spinal anaesthesia for Caesarean section, Patel, M., *et al.*, (*C*) 662
——, Spinal anaesthesia for Caesarean section, Russell, I. F., *et al.*, (*C*) 662
——, Spinal anaesthesia for Caesarean section: comparison of 22-gauge and 25-gauge Whiteacre needles with 26-gauge Quincke needles, Shutt, L. E., *et al.* 589–594
——, Spread of spinal anaesthesia, Adkisson, G. H., (*C*) 328
——, Spread of spinal anaesthesia, Tuominen, M., *et al.*, (*C*) 328–329
——, Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway, Philips, B. J., *et al.* 407–408
Anaesthetic techniques, subconvulsive dose, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects on circulatory function, Huang, Y. F., *et al.* 368–374
Anaesthetic techniques, topical, Application of EMLA before extradural insertion in labour, Ralston, S. J., *et al.*, (*ARS*) 220–221P
——, Topical anaesthesia for extracorporeal shock wave lithotripsy, McDonald, P. F., *et al.* 399–400
Anaesthetics gases, nitrous oxide, Influence of vitamin B_{12} status on the inactivation of methionine synthase by nitrous oxide, Landon, M. J., *et al.* 81–86
Anaesthetics i.v., etomidate, Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate, Price, M. L., *et al.* 172–176
——, Does etomidate cause haemolysis? Nebauer, A. E., *et al.* 58–60
——, Etomidate shortens the onset time of neuromuscular block, Gill, R. S., *et al.* 444–446
——, Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum, Esener, Z., *et al.* 586–588
Anaesthetics i.v., ketamine, Action of ketamine on isolated porcine trachealis muscle, Hatch, D. J., *et al.*, (*ARS*) 217P
——, Molecular actions of racemic ketamine on human CNS sodium channels, Frenkel, C., *et al.* 292–297
Anaesthetics i.v., methohexitone, Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate, Price, M. L., *et al.* 172–176
——, Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery, Lange, H., *et al.* 478–481
——, Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion, Bethune, D. W., *et al.* 197–199
Anaesthetics i.v., morphine, Effect of four different maintenance anaesthetic techniques for minor surgery on gastric emptying, Bennett, M. W. R., *et al.*, (*ARS*) 220P
——, Extradural fentanyl–bupivacaine compared with patient controlled analgesia using i.v. morphine after upper abdominal surgery, Wright, P. M. C., *et al.*, (*ARS*) 219–220P
Anaesthetics i.v., propofol, Anaphylactoid or carcinoid? Batchelor, A. M., *et al.* 325–327
——, Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate, Price, M. L., *et al.* 172–176
——, Comparison of propofol–fentanyl and isoflurane–fentanyl for maintenance of anaesthesia during cardiac surgery, Phillips, A. S., *et al.*, (*ARS*) 211–212P
——, Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin, O'Donnell, N. G., *et al.* 70–74
——, EEG and memory effects of low-dose infusions of propofol, Veselis, R. A., *et al.* 246–254
——, EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects, Laycock, G. J. A., *et al.* 356–362
——, Effect of four different maintenance anaesthetic techniques for minor surgery on gastric emptying, Bennett, M. W. R., *et al.*, (*ARS*) 220P
——, Effect of graded infusion rates of propofol on regional and global left ventricular function in the dog, Puttick, R. M., *et al.* 375–381
——, Effect of propofol and thiopentone on free radical-induced haemolysis, Murphy, P. G., *et al.*, (*ARS*) 532–533P
——, Etomidate shortens the onset time of neuromuscular block, Gill, R. S., *et al.* 444–446
——, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64
——, Four anaesthetic techniques for day-case oral surgery, Martlew, R., *et al.*, (*ARS*) 219P
——, Haemodynamic effects of isoflurane during propofol anaesthesia, Verborgh, C., *et al.* 36–39
——, Heart rate spectrum analysis during induction of anaesthesia with thiopentone or propofol, Howell, S., *et al.*, (*ARS*) 536P
——, Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol, Murray, J. M., *et al.* 643–644
——, Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil, Short, T. G., *et al.* 162–167
——, Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients, Peacock, J. E., *et al.* 363–367
——, Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion, Bethune, D. W., *et al.* 197–199
——, Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol, Barker, P., *et al.* 23–25
——, Pain on the injection of propofol: comparison of lignocaine with metoclopramide, Ganta, R., *et al.* 316–317
——, Pharmacodynamic stability of a mixture of propofol and alfentanil, Taylor, I. N., *et al.* 168–171
——, Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia, Browne, B. L., *et al.* 570–576
——, Propofol anticonvulsant activity in experimental epileptic status, De Riu, P. L., *et al.* 177–181
——, Propofol in uraemic patients, Lewis, I. H., *et al.*, (*C*) 329
——, Synergistic interaction between midazolam and propofol, McClune, S., *et al.* 240–245
——, Vocal cord movement on induction of anaesthesia, Fink, B. R., (*C*) 661
——, Vocal cord movement on induction of anaesthesia, Langton, J., *et al.*, (*C*) 661–662
Anaesthetics i.v., thiamylal, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64
Anaesthetics i.v., thiopentone, Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate, Price, M. L., *et al.* 172–176
——, Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin, O'Donnell, N. G., *et al.* 70–74
——, Effect of propofol and thiopentone on free radical-induced haemolysis, Murphy, P. G., *et al.*, (*ARS*) 532–533P
——, Etomidate shortens the onset time of neuromuscular block, Gill, R. S., *et al.* 444–446
——, Heart rate spectrum analysis during induction of anaesthesia with thiopentone or propofol, Howell, S., *et al.*, (*ARS*) 536P
——, Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol, Barker, P., *et al.* 23–25
——, Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum, Esener, Z., *et al.* 586–588

——, Vocal cord movement on induction of anaesthesia, Fink, B. R., (*C*) 661

——, Vocal cord movement on induction of anaesthesia, Langton, J., *et al.*, (*C*) 661–662

Anaesthetics local, Pre-emptive analgesia, McQuay, H. J., (*E*) 1–3

Anaesthetics local, bupivacaine, Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine, Tehan, B. 520–521

——, Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia, Eddleston, J. M., *et al.* 154–158

——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.* 634–636

——, Effect of speed of injection of 0.5% plain bupivacaine on the spread of spinal anaesthesia, Tuominen, M., *et al.* 148–149

——, Elimination of bupivacaine and pethidine from the rabbit feto–placental unit, Carson, R. J., *et al.* 150–153

——, Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs, Finegan, B. A., *et al.* 492–497

——, Extradural fentanyl–bupivacaine compared with patient controlled analgesia using i.v. morphine after upper abdominal surgery, Wright, P. M. C., *et al.*, (*ARS*) 219–220P

——, Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery, Dahl, J. B., *et al.* 4–8

——, Intrathecal diamorphine–bupivacaine during labour, Kestin, I. G., (*C*) 108

——, Intrathecal diamorphine–bupivacaine during labour, Scott, P. V., *et al.*, (*C*) 108

——, Intrathecal morphine-6-glucuronide and bupivacaine for postoperative pain, Coe, A. J., *et al.*, (*ARS*) 221P

——, Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic, Blumgart, C. H., *et al.* 457–460

——, Pre-emptive extradural analgesia, Dahl, J. B., *et al.*, (*C*) 664–665

——, Pre-emptive extradural analgesia, Wilder-Smith, O. H. G., *et al.*, (*C*) 663–664

——, Spinal anaesthesia for Caesarean section, Patel, M., *et al.*, (*C*) 662

——, Spinal anaesthesia for Caesarean section, Russell, I. F., *et al.*, (*C*) 662

——, Spread of spinal anaesthesia, Adkisson, G. H., (*C*) 328

——, Spread of spinal anaesthesia, Tuominen, M., *et al.*, (*C*) 328–329

Anaesthetics local, EMLA, Application of EMLA before extradural insertion in labour, Ralston, S. J., *et al.*, (*ARS*) 220–221P

——, Topical anaesthesia for extracorporeal shock wave lithotripsy, McDonald, P. F., *et al.* 399–400

Anaesthetics local, lignocaine, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects on circulatory function, Huang, Y. F., *et al.* 368–374

——, Pain on the injection of propofol: comparison of lignocaine with metoclopramide, Ganta, R., *et al.* 316–317

——, Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery, Michael, S., *et al.* 577–579

——, Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure, Putensen, C., *et al.* 513–516

——, Pressor response to venous cannulation and effect of local anaesthetic infiltration, Langham, B. T., *et al.*, (*ARS*) 537–538P

Anaesthetics volatile, desflurane, Recovery of cognitive functions after anaesthesia with desflurane or isoflurane and nitrous oxide, Tsai, S. K., *et al.* 255–258

Anaesthetics volatile, enflurane, Breakdown of halogenated inhalation anaesthetic agents with water vapour in breathing systems, Beatty, P. C. W., *et al.*, (*ARS*) 216P

——, Effect of four different maintenance anaesthetic techniques for minor surgery on gastric emptying, Bennett, M. W. R., *et al.*, (*ARS*) 220P

——, Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia, Mayer, M., *et al.* 511–512

Anaesthetics volatile, halothane, A National Database on hepatitis after exposure to inhaled anaesthetics, Kenna, J. G., *et al.*, (*C*) 228–229

——, Breakdown of halogenated inhalation anaesthetic agents with water vapour in breathing systems, Beatty, P. C. W., *et al.*, (*ARS*) 216P

——, Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium, Parker, C. J. R., *et al.* 439–443

——, Effect of halothane on [^{3}H]methylcholine uptake into rat brain synaptosomes, Griffiths, R., *et al.*, (*ARS*) 530P

——, Effects of halothane on cultured neurones, Winlow, W., *et al.*, (*ARS*) 530–531P

——, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64

——, Halothane-induced changes in intracellular calcium ion concentration in neurones from *Lymnaea stagnalis*, Hopkins, P. M., *et al.*, (*ARS*) 210–211P

——, Halothane produces potent endothelium-independent vasodilatation in canine middle cerebral arteries, Flynn, N. M., *et al.*, (*ARS*) 210P

——, Inhibition of sodium–calcium exchange increases skeletal muscle contracture response to halothane, Hopkins, P. M., *et al.*, (*ARS*) 531–532P

——, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, Micol, J. A., *et al.* 487–491

——, Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? Ellis, F. R., *et al.* 468–470

——, Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery, Stühmeier, K. D., *et al.* 602–606

Anaesthetics volatile, isoflurane, Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane, Newton, D. E. F., *et al.* 122–129

——, Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia, Katoh, T., *et al.* 259–262

——, Breakdown of halogenated inhalation anaesthetic agents with water vapour in breathing systems, Beatty, P. C. W., *et al.*, (*ARS*) 216P

——, Coherence in the auditory evoked response as a measure of arousal during anaesthesia, Sapsford, D. J., *et al.*, (*ARS*) 538P

——, Comparison of propofol–fentanyl and isoflurane–fentanyl for maintenance of anaesthesia during cardiac surgery, Phillips, A. S., *et al.*, (*ARS*) 211–212P

——, Components of the inspired to arterial isoflurane partial pressure difference, Matson, A. M., *et al.*, (*ARS*) 528–529P

——, Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium, Parker, C. J. R., *et al.* 439–443

——, Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam–fentanyl or isoflurane anaesthesia, Olsen, K. S., *et al.* 263–268

——, Effects of isoflurane anaesthesia on the median nerve somatosensory evoked potential in children, Mason, D. G., *et al.* 562–566

——, Four anaesthetic techniques for day-case oral surgery, Martlew, R., *et al.*, (*ARS*) 219P

——, Haemodynamic effects of isoflurane during propofol anaesthesia, Verborgh, C., *et al.* 36–39

——, Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery, Stühmeier, K. D., *et al.* 602–606

——, Isoflurane inhibits insulin secretion from isolated rat pancreatic islets of Langerhans, Desborough, J. P., *et al.*, (*ARS*) 532P

——, Recovery of cognitive functions after anaesthesia with desflurane or isoflurane and nitrous oxide, Tsai, S. K., *et al.* 255–258

——, Sequential measurement of the median nerve somatosensory evoked potential during isoflurane anaesthesia in children, Mason, D. G., *et al.* 567–569

——, Somatic movement and oesophageal motility during isoflurane anaesthesia, Mather, C., *et al.* 40–44

——, Some effects of isoflurane on I waves of the motor evoked potential, Hicks, R. G., *et al.* 130–136

——, Sternocleidomastoid muscle contractility at different levels of isoflurane anaesthesia in humans, Oshima, T., *et al.* 236–239

Anaesthetics volatile, sevoflurane, Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia, Katoh, T., *et al.* 259–262

Anaesthetist, activity, Perioperative blood loss and its reduction: the role of the anaesthetist, Simpson, P. 498–507

Analeptics, caffeine, Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? Ellis, F. R., *et al.* 468–470

Analgesia, obstetric, Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine, Tehan, B. 520–521

——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.* 634–636
Analgesia, patient-controlled, Extradural fentanyl–bupivacaine compared with patient controlled analgesia using i.v. morphine after upper abdominal surgery, Wright, P. M. C., *et al.*, (*ARS*) 219–220P
——, Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia, Madej, T. H., *et al.* 554–557
——, Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia, Wheatley, R. G., *et al.* 558–561
——, Overdose of opioid from patient-controlled analgesia pumps, Notcutt, W. G., *et al.* 95–97
——, Patient-controlled analgesia after thoracotomy: thoracic extradural *vs* i.v. fentanyl, Keenan, G. M. A., *et al.*, (*ARS*) 533P
——, Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy, Merry, A. F., *et al.* 92–94
Analgesia, postoperative, Ketorolac trometamol for postoperative analgesia after orthopaedic surgery, Kinsella, J., *et al.* 19–22
——, Overdose of opioid from patient-controlled analgesia pumps, Notcutt, W. G., *et al.* 95–97
——, Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy, Merry, A. F., *et al.* 92–94
Analgesia, pre-emptive, Pre-emptive analgesia, McQuay, H. J., (*E*) 1–3
——, Pre-emptive extradural analgesia, Dahl, J. B., *et al.*, (*C*) 664–665
——, Pre-emptive extradural analgesia, Wilder-Smith, O. H. G., *et al.*, (*C*) 663–664
Analgesia, preoperative, Pain on the injection of propofol: comparison of lignocaine with metoclopramide, Ganta, R., *et al.* 316–317
Analgesic techniques, extradural, Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia, Eddleston, J. M., *et al.* 154–158
——, Delayed septicaemia after extradural steroid treatment, Elliott, R. H., *et al.*, (*C*) 422
——, Delayed septicaemia after extradural steroid treatment, Scriven, M. W., *et al.*, (*C*) 422–423
——, Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia, Madej, T. H., *et al.* 554–557
——, Patient-controlled analgesia after thoracotomy: thoracic extradural *vs* i.v. fentanyl, Keenan, G. M. A., *et al.*, (*ARS*) 533P
——, Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure, Putensen, C., *et al.* 513–516
——, Pre-emptive extradural analgesia, Dahl, J. B., *et al.*, (*C*) 664–665
——, Pre-emptive extradural analgesia, Wilder-Smith, O. H. G., *et al.*, (*C*) 663–664
——, Steroid therapy and extradural analgesia, Ngan Kee, W. D., (*C*) 423
Analgesic techniques, i.m., Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia, Wheatley, R. G., *et al.* 558–561
Analgesic techniques, i.v., Patient-controlled analgesia after thoracotomy: thoracic extradural *vs* i.v. fentanyl, Keenan, G. M. A., *et al.*, (*ARS*) 533P
Analgesic techniques, subarachnoid, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.* 634–636
——, Intrathecal morphine-6-glucuronide and bupivacaine for postoperative pain, Coe, A. J., *et al.*, (*ARS*) 221P
Analgesics anti-inflammatory, steroid, Delayed septicaemia after extradural steroid treatment, Elliott, R. H., *et al.*, (*C*) 422
——, Delayed septicaemia after extradural steroid treatment, Scriven, M. W., *et al.*, (*C*) 422–423
——, Steroid therapy and extradural analgesia, Ngan Kee, W. D., (*C*) 423
Analgesics non-opioid, aspirin, Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), Macdonald, R., (*C*) 109–110
——, Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), de Swiet, M., *et al.*, (*C*) 109
Analgesics non-opioid, diclofenac, Effect of diclofenac on renal function and prostacyclin generation after surgery, Power, I., *et al.* 451–456
——, Venous sequelae of diclofenac, Berry, C. B., *et al.*, (*C*) 332
——, Venous sequelae of diclofenac, Gopinath, R., (*C*) 332
Analgesics non-opioid, indomethacin, Indomethacin in the management of postoperative pain, Nissen, I., *et al.* 304–306
Analgesics non-opioid, ketorolac, Ketorolac trometamol for postoperative analgesia after orthopaedic surgery, Kinsella, J., *et al.* 19–22
Analgesics non-opioid, tenoxicam, Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy, Merry, A. F., *et al.* 92–94
Analgesics opioid, Pre-emptive analgesia, McQuay, H. J., (*E*) 1–3
Analgesics opioid, alfentanil, Disposition of alfentanil in burns patients, McFie, A. G., *et al.* 447–450
——, Effect of four different maintenance anaesthetic techniques for minor surgery on gastric emptying, Bennett, M. W. R., *et al.*, (*ARS*) 220P
——, Effect of preoperative opioid administration on postoperative pain, Dahl, J. B., *et al.*, (*C*) 424–425
——, Effect of preoperative opioid administration on postoperative pain, Katz, J., *et al.*, (*C*) 424
——, Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil, Short, T. G., *et al.* 162–167
——, Pharmacodynamic stability of a mixture of propofol and alfentanil, Taylor, I. N., *et al.* 168–171
——, Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia, Browne, B. L., *et al.* 570–576
Analgesics opioid, diamorphine, Intrathecal diamorphine–bupivacaine during labour, Kestin, I. G., (*C*) 108
——, Intrathecal diamorphine–bupivacaine during labour, Scott, P. V., *et al.*, (*C*) 108
——, Overdose of opioid from patient-controlled analgesia pumps, Notcutt, W. G., *et al.* 95–97
Analgesics opioid, fentanyl, Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine, Tehan, B. 520–521
——, Comparison of propofol–fentanyl and isoflurane–fentanyl for maintenance of anaesthesia during cardiac surgery, Phillips, A. S., *et al.*, (*ARS*) 211–212P
——, Effect of fentanyl on ventilatory resistances during barbiturate general anaesthesia, Cohendy, R., *et al.* 595–598
——, Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam–fentanyl or isoflurane anaesthesia, Olsen, K. S., *et al.* 263–268
——, Extradural fentanyl–bupivacaine compared with patient controlled analgesia using i.v. morphine after upper abdominal surgery, Wright, P. M. C., *et al.*, (*ARS*) 219–220P
——, Fentanyl inhibits evoked [^{3}H]noradrenaline release from human neuroblastoma cells, Atcheson, R., *et al.*, (*ARS*) 531P
——, Patient-controlled analgesia after thoracotomy: thoracic extradural *vs* i.v. fentanyl, Keenan, G. M. A., *et al.*, (*ARS*) 533P
——, Respiratory depression after extradural fentanyl, Wang, C. Y., (*C*) 544
Analgesics opioid, morphine, Comparison of extradural administration of sufentanil, morphine and sufentanil–morphine combination after Caesarean section, Dottrens, M., *et al.* 9–12
——, Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy, Welte, M., *et al.* 637–639
——, Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery, Dahl, J. B., *et al.* 4–8
——, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, Micol, J. A., *et al.* 487–491
——, Ketorolac trometamol for postoperative analgesia after orthopaedic surgery, Kinsella, J., *et al.* 19–22
——, One-compartment kinetics, Norman, J. 387–396
——, Pre-emptive extradural analgesia, Dahl, J. B., *et al.*, (*C*) 664–665
——, Pre-emptive extradural analgesia, Wilder-Smith, O. H. G., *et al.*, (*C*) 663–664
Analgesics opioid, morphine-6-glucuronide, Intrathecal morphine-6-glucuronide and bupivacaine for postoperative pain, Coe, A. J., *et al.*, (*ARS*) 221P
Analgesics opioid, pethidine, Elimination of bupivacaine and pethidine from the rabbit feto-placental unit, Carson, R. J., *et al.* 150–153

Analgesics opioid, sufentanil, Comparison of extradural administration of sufentanil, morphine and sufentanil–morphine combination after Caesarean section, Dottrens, M., *et al.* 9–12

Anesthesiology Review, Faust, R. J., (editor), (*R*) 230–231

Antacids, famotidine, Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery, Escolano, F., *et al.* 404–406

Antacids, omeprazole, Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery, Escolano, F., *et al.* 404–406

Antacids, ranitidine, Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery, Escolano, F., *et al.* 404–406

Antagonists benzodiazepine, flumazenil, EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism, Engelhardt, W., *et al.* 75–80

——, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64

——, Midazolam and cardioversion, Gupta, A., *et al.*, (*C*) 422

Antagonists, miscellaneous, 5-HT$_3$ antagonists and postoperative nausea and vomiting, Russell, D., *et al.* 63–68S

——, Postoperative nausea and vomiting in day-case surgery, Wetchler, B. V. 33–39S

Antagonists neuromuscular block, neostigmine, Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly, McCarthy, G. J., *et al.* 281–283

Antagonists opioid, naloxone, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, Micol, J. A., *et al.* 487–491

Anticonvulsants, Propofol anticonvulsant activity in experimental epileptic status, De Riu, P. L., *et al.* 177–181

Arterial pressure, drug effects, Effect of rocuronium and vecuronium on intraocular pressure, Hull, J. M., *et al.*, (*ARS*) 534P

——, Pressor response to venous cannulation and effect of local anaesthetic infiltration, Langham, B. T., *et al.*, (*ARS*) 537–538P

Arterial pressure, hypertension, Preoperative silent ischaemia is related to hypertension, Muir, A. D., *et al.*, (*ARS*) 540P

Arterial pressure, hypertension, aspirin, Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects, Orlikowski, C. E. P., *et al.* 159–161

Arterial pressure, regulation automatic, Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma, Chaudhri, S., *et al.* 607–610

Arteries, axillary, Fatal tracheal compression after haemorrhage into the axilla, Cook, L. B., *et al.* 322–324

Arteries, cannulation, Accuracy of coagulation studies performed on blood samples obtained from arterial cannulae, Haynes, S. R., *et al.* 599–601

Arteries, cerebral, Halothane produces potent endothelium-independent vasodilatation in canine middle cerebral arteries, Flynn, N. M., *et al.*, (*ARS*) 210P

——, Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin F$_{2\alpha}$ in isolated human pial arteries, Reinstrup, P., *et al.* 615–620

Assessment, preanaesthetic, Antenatal assessment for anaesthesia, Cody, M. W., *et al.*, (*C*) 332

Ataractics, butyrophenones, Current management of postoperative nausea and vomiting, Rowbotham, D. J. 46–59S

Ataractics, phenothiazines, Current management of postoperative nausea and vomiting, Rowbotham, D. J. 46–59S

Atlas of Regional Anaesthesia, Brown, D. L., (*R*) 426

Atlas of the Difficult Airway, Brown, A. C. D., *et al.*, (*R*) 231

Biology, biochemistry, Massive blood transfusion, Donaldson, M. D. J., *et al.* 621–630

Blood, anaesthetic concentration, Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia, Katoh, T., *et al.* 259–262

——, Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure, Putensen, C., *et al.* 513–516

——, Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum, Esener, Z., *et al.* 586–588

Blood, anticoagulants, heparin, Accuracy of coagulation studies performed on blood samples obtained from arterial cannulae, Haynes, S. R., *et al.* 599–601

Blood, coagulation, Accuracy of coagulation studies performed on blood samples obtained from arterial cannulae, Haynes, S. R., *et al.* 599–601

——, Bleeding time, Bromage, P. R., (*C*) 330

——, Bleeding time, McDonald, R., (*C*) 329

——, Bleeding time, O'Kelly, S. W., *et al.*, (*C*) 330–331

——, Bleeding time, Power, I., (*C*) 329–330

——, Massive blood transfusion, Donaldson, M. D. J., *et al.* 621–630

——, Perioperative blood loss and its reduction: the role of the anaesthetist, Simpson, P. 498–507

——, Thrombelastography, Mallett, S. V., *et al.* 307–313

——, Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects, Orlikowski, C. E. P., *et al.* 159–161

Blood, erythrocytes, Effect of propofol and thiopentone on free radical-induced haemolysis, Murphy, P. G., *et al.*, (*ARS*) 532–533P

——, Plasma antioxidant activity in stored blood, Myers, D. S., *et al.*, (*ARS*) 222P

Blood, flow, skin, Effects of skin blood flow and temperature on skin–electrode impedance and offset potential, Smith, D. C., (*ARS*) 223P

Blood, haemoglobin, Unnecessary preoperative investigations in children, Wilson, A., *et al.*, (*C*) 425

Blood, haemolysis, Does etomidate cause haemolysis? Nebauer, A. E., *et al.* 58–60

——, Effect of propofol and thiopentone on free radical-induced haemolysis, Murphy, P. G., *et al.*, (*ARS*) 532–533P

Blood, leucocytes, General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients, Samsoon, G., *et al.* 653–656

Blood, loss, Blood loss during total hip replacement, McSwiney, M., *et al.*, (*C*) 331–332

——, Blood loss during total hip replacement, Wittmann, P. H., *et al.*, (*C*) 332

——, Perioperative blood loss and its reduction: the role of the anaesthetist, Simpson, P. 498–507

Blood, neutrophils, Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin, O'Donnell, N. G., *et al.* 70–74

——, Influence of myocardial preservation technique on perioperative neutrophil activity in patients undergoing coronary artery graft surgery, Columb, M. O., *et al.*, (*ARS*) 211P

Blood, platelets, Bleeding time, McDonald, R., (*C*) 329

Blood, transfusion, Blood loss during total hip replacement, McSwiney, M., *et al.*, (*C*) 331–332

——, Blood loss during total hip replacement, Wittmann, P. H., *et al.*, (*C*) 332

——, Massive blood transfusion, Donaldson, M. D. J., *et al.* 621–630

Blood, volume, Comparison of hypertonic saline (5%), isotonic saline and Ringer's lactate solutions for fluid preloading before lumbar extradural anaesthesia, Veroli, P., *et al.* 461–464

——, Massive blood transfusion, Donaldson, M. D. J., *et al.* 621–630

Book Reviews

Adult Respiratory Distress Syndrome, Artigas, A., *et al.*, (editors), (*R*) 427

Advances in Pain Research and Therapy, Volume 18: The Design of Analgesic Clinical Trials, Max, M. B., *et al.*, (editors), (*R*) 230

Anaesthesia for Ophthalmic and Otolaryngologic Surgery, McGoldrick, E., (editor), (*R*) 667

Anesthesiology Review, Faust, R. J., (editor), (*R*) 230–231

Atlas of Regional Anaesthesia, Brown, D. L., (*R*) 426

Atlas of the Difficult Airway, Brown, A. C. D., *et al.*, (*R*) 231

Clinical Practice of Regional Anesthesia, Prithvi Raj, P., (editor), (*R*) 546–547

Critical Care Toxicology (*Contemporary Management in Critical Care* series), Hoffman, R. S., *et al.*, (editors), (*R*) 547

Dripps/Eckenhoff/Vandam Introduction to Anaesthesia, 8th Edn, Longnecker, D. E., *et al.*, (editors), (*R*) 231

Drug Infusions in Anesthesiology, Fragen, R. J., (editor), (*R*) 112

Emergency Medicine and the Anaesthetist (*Baillière's Clinical Anaesthesiology* series), Delooz, H. H., (editor), (*R*) 546

Infection and the Anaesthetist, Stoutenbeek, C. P., *et al.*, (editors), (*R*) 112–113

Kinetics of Anaesthetic Drugs in Clinical Anesthesiology,

White, P. F., (editor), (*R*) 667
Lecture Notes on Anaesthetics, 4th Edn, Lunn, J. N., (*R*) 113
Manual of Obstetric Anesthesia, 2nd Edn, Ostheimer, G. W., (editor), (*R*) 547–548
Manual of Post-Anesthesia Care, Jacobsen, W. K., *et al.*, (editors), (*R*) 333–334
Maternal Mortality—The Way Forward. Some Implications of the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–87, Patel, N., (editor), (*R*) 547
MCQ Companion to the Textbook of Anaesthesia, Fell, D., *et al.*, (*R*) 667–668
MCQ for the Higher Examinations in Clinical Pharmacology, McCarthy, G., *et al.*, (*R*) 546
Mechanical Ventilation and Assisted Respiration, Grenvik, A., *et al.*, (editors), (*R*) 334
Plasma Volume Expansion, Baron, J.-F., (editor), (*R*) 668
Principles of Measurement and Monitoring in Anaesthesia and Intensive Care, 3rd Edn, Sykes, M. K., *et al.*, (*R*) 666
Researches Practical and Physiological on Etherization, Pirogoff, N., *et al.*, (*R*) 333
Respiratory Monitoring (*Contemporary Management in Critical Care* series), Tobin, M. J., (editor), (*R*) 666
Standard Operating Procedures for Investigators, Ball, G., *et al.*, (*R*) 231
Standards of Care in Anaesthesia, Taylor, T. H., *et al.*, (*R*) 334
The Ageing Surgical Patient—Anaesthetic, Operative and Medical Management, Crosby, D. L., *et al.*, (editors), (*R*) 426–427
The Critical Care Drug Handbook, Zaloga, G. P., (*R*) 548
The Management of Acute Pain, Park, G., *et al.*, (*R*) 548
The Obstructed Airway (Ministry of Defence training film), (*R*) 427
The Oxygen Status of Arterial Blood, Zander, R., *et al.*, (editors), (*R*) 333
The Pediatric Anesthesia Handbook, Bell, C., *et al.*, (editors), (*R*) 230
Thoracic Anesthesia, 2nd Edn, Kaplan, J. A., (editor), (*R*) 112
Year Book of Anesthesia, 1991, Miller, R. D., *et al.*, (editors), (*R*) 113
Brain, blood–brain barrier, Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood–brain barrier, Werba, A., *et al.* 382–386
Brain, blood flow, Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome, Stephan, H., *et al.* 51–57
——, Comparison of the effects of methoxamine and phenylephrine on middle cerebral artery velocity during carotid endarterectomy, Kaneko, K., *et al.*, (*ARS*) 537P
——, Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam–fentanyl or isoflurane anaesthesia, Olsen, K. S., *et al.* 263–268
——, Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin F$_{2\alpha}$ in isolated human pial arteries, Reinstrup, P., *et al.* 615–620
Brain, electroencephalography, EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism, Engelhardt, W., *et al.* 75–80
——, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64
Brain, evoked potentials, Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane, Newton, D. E. F., *et al.* 122–129
——, EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism, Engelhardt, W., *et al.* 75–80
——, Effects of isoflurane anaesthesia on the median nerve somatosensory evoked potential in children, Mason, D. G., *et al.* 562–566
——, Sequential measurement of the median nerve somatosensory evoked potential during isoflurane anaesthesia in children, Mason, D. G., *et al.* 567–569
Brain, metabolism, Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome, Stephan, H., *et al.* 51–57
Brain, oxygen consumption, Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam–fentanyl or isoflurane anaesthesia, Olsen, K. S., *et al.* 263–268
Brain, synapses, Effect of halothane on [^{3}H]methylcholine uptake into rat brain synaptosomes, Griffiths, R., *et al.*, (*ARS*) 530P
——, Molecular actions of racemic ketamine on human CNS sodium channels, Frenkel, C., *et al.* 292–297
Burns, Disposition of alfentanil in burns patients, McFie, A. G., *et al.* 447–450

Calcium channel block, diltiazem, Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs, Finegan, B. A., *et al.* 492–497
Cancer, Anaesthetic management of renin secreting nephroblastoma, Charlton, G. A., *et al.* 206–209
——, Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma, Chaudhri, S., *et al.* 607–610
——, Repeated resistance to non-depolarizing neuromuscular blocking drugs in a patient with multiple myeloma, Ip Yam, C., *et al.*, (*C*) 111
Carbon dioxide, elimination, Control of carbon dioxide in circle systems, McHale, S. P., *et al.*, (*ARS*) 529P
Carbon dioxide, partial pressure, Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin F$_{2\alpha}$ in isolated human pial arteries, Reinstrup, P., *et al.* 615–620
——, Ventilatory effects of laparoscopy under general anaesthesia, Puri, G. D., *et al.*, (*C*) 543
——, Ventilatory effects of laparoscopy under general anaesthesia, Shankar, K. B., *et al.*, (*C*) 542–543
Carbon dioxide, rebreathing, Determination of the onset of rebreathing: comparison of six methods during spontaneous ventilation, Barrie, J. R., *et al.*, (*ARS*) 527P
——, Oxygen uptake during rebreathing in a Mapleson A system, Campkin, N., *et al.*, (*ARS*) 538P
——, Rebreathing in the Magill breathing system, Soni, N., *et al.*, (*ARS*) 215–216P
Cardiorespiratory system, effects, Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients, Peacock, J. E., *et al.* 363–367
Cardiovascular system, effects, Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs, Finegan, B. A., *et al.* 492–497
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects on circulatory function, Huang, Y. F., *et al.* 368–374
Cardiovascular system, responses, Atracurium and histamine, Adt, M., (*C*) 110
——, Atracurium and histamine, Scott, R. P. F., (*C*) 110
——, Cardiovascular responses to tracheal extubation, Dhamee, M. S., *et al.*, (*C*) 229
——, Cardiovascular responses to tracheal extubation, Fell, D., *et al.*, (*C*) 229
——, Comparison of propofol–fentanyl and isoflurane–fentanyl for maintenance of anaesthesia during cardiac surgery, Phillips, A. S., *et al.*, (*ARS*) 211–212P
——, EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects, Laycock, G. J. A., *et al.* 356–362
——, Effect of diabetic autonomic dysfunction on the cardiovascular responses to induction of anaesthesia and tracheal intubation, Vohra, A., *et al.*, (*ARS*) 212–213P
——, Haemodynamic effects of isoflurane during propofol anaesthesia, Verborgh, C., *et al.* 36–39
——, Pressor response to venous cannulation and effect of local anaesthetic infiltration, Langham, B. T., *et al.*, (*ARS*) 537–538P
——, The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses, Lamb, K., *et al.* 143–147
——, Ventilatory effects of laparoscopy under general anaesthesia, Puri, G. D., *et al.*, (*C*) 543
——, Ventilatory effects of laparoscopy under general anaesthesia, Shankar, K. B., *et al.*, (*C*) 542–543
——, Verapamil and cardiovascular responses to tracheal intubation, Nishikawa, T., (*C*) 225
——, Verapamil and cardiovascular responses to tracheal intubation, Yaku, H., *et al.*, (*C*) 225–226
Cerebrospinal fluid, Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood–brain barrier, Werba, A., *et al.* 382–386
Children, Anaesthesia for critically ill children during magnetic resonance imaging, Tobin, J. R., *et al.* 482–486
——, EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects, Laycock, G. J. A., *et al.* 356–362

——, Effects of isoflurane anaesthesia on the median nerve somatosensory evoked potential in children, Mason, D. G., *et al.* 562–566
——, Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery, Michael, S., *et al.* 577–579
——, Postoperative nausea and vomiting in day-case surgery, Wetchler, B. V. 33–39S
——, Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia, Browne, B. L., *et al.* 570–576
——, Sequential measurement of the median nerve somatosensory evoked potential during isoflurane anaesthesia in children, Mason, D. G., *et al.* 567–569
——, Unnecessary preoperative investigations in children, Wilson, A., *et al.*, (*C*) 425
Clinical Practice of Regional Anesthesia, Prithvi Raj, P., (editor), (*R*) 546–547
Colostrum, anaesthetic concentration, Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum, Esener, Z., *et al.* 586–588
Complications, adult respiratory distress syndrome, General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients, Samsoon, G., *et al.* 653–656
Complications, anaemia, Unnecessary preoperative investigations in children, Wilson, A., *et al.*, (*C*) 425
Complications, anaphylaxis, Anaphylactoid or carcinoid? Batchelor, A. M., *et al.* 325–327
——, Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs, Laroche, D., *et al.* 611–614
——, Radioimmunoassay tests and anaphylaxis, Imray, I. McG., *et al.*, (*C*) 543–544
Complications, arrhythmia, Transient bradycardia associated with extradural blood patch after inadvertent dural puncture in parturients, Andrews, P. J. D., *et al.* 401–403
Complications, aspiration, Cricoid pressure may prevent insertion of the laryngeal mask airway, Ansermino, J. M., *et al.* 465–467
——, Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery, Escolano, F., *et al.* 404–406
Complications, backache, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.* 414–416
——, Spinal anaesthesia for Caesarean section: comparison of 22-gauge and 25-gauge Whiteacre needles with 26-gauge Quincke needles, Shutt, L. E., *et al.* 589–594
Complications, breakdown products, Breakdown of halogenated inhalation anaesthetic agents with water vapour in breathing systems, Beatty, P. C. W., *et al.*, (*ARS*) 216P
Complications, carcinoid syndrome, Anaphylactoid or carcinoid? Batchelor, A. M., *et al.* 325–327
Complications, catheter migration, Continuous subarachnoid infusion of local anaesthetic, Morton, C. P. J., *et al.*, (*ARS*) 533P
Complications, coagulopathy, General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients, Samsoon, G., *et al.* 653–656
Complications, convulsions, Propofol anticonvulsant activity in experimental epileptic status, De Riu, P. L., *et al.* 177–181
Complications, death, Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery, Stühmeier, K. D., *et al.* 602–606
——, The National Confidential Enquiry into Perioperative Deaths 1990, Graham, S. G., (*E*) 431–432
Complications, diabetes, Effect of diabetic autonomic dysfunction on the cardiovascular responses to induction of anaesthesia and tracheal intubation, Vohra, A., *et al.*, (*ARS*) 212–213P
Complications, drug resistance, Probable resistance to vecuronium involving the 17-hydroxy metabolite, Cozanitis, D. A., (*C*) 110–111
——, Repeated resistance to non-depolarizing neuromuscular blocking drugs in a patient with multiple myeloma, Ip Yam, C., *et al.*, (*C*) 111
Complications, dural puncture, Accidental subdural catheterization: radiological evidence of a possible mechanism for spinal cord damage, McMenemin, I. M., *et al.* 417–419
——, Transient bradycardia associated with extradural blood patch after inadvertent dural puncture in parturients, Andrews, P. J. D., *et al.* 401–403
Complications, Ehlers–Danlos type IV, Anaesthesia for Caesarean section in a patient with Ehlers–Danlos syndrome type IV, Brighouse, D., *et al.* 517–519
Complications, extradural abscess, Extradural abscess complicating extradural anaesthesia for Caesarean section, Ngan Kee, W. D., *et al.* 647–652
——, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.* 414–416
——, Steroid therapy and extradural analgesia, Ngan Kee, W. D., (*C*) 423
Complications, haemolysis, Does etomidate cause haemolysis? Nebauer, A. E., *et al.* 58–60
Complications, haemorrhage, Fatal tracheal compression after haemorrhage into the axilla, Cook, L. B., *et al.* 322–324
——, Perioperative blood loss and its reduction: the role of the anaesthetist, Simpson, P. 498–507
Complications, headache, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.* 414–416
——, Postdural puncture headache in urological surgery: an evaluation of the atraumatic spinal needle, Harrison, D. A., *et al.*, (*ARS*) 540–541P
——, Spinal anaesthesia for Caesarean section: comparison of 22-gauge and 25-gauge Whiteacre needles with 26-gauge Quincke needles, Shutt, L. E., *et al.* 589–594
——, Transient bradycardia associated with extradural blood patch after inadvertent dural puncture in parturients, Andrews, P. J. D., *et al.* 401–403
Complications, histamine release, *In vitro* displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs, Williams, W. R., *et al.* 508–510
Complications, hypereosinophilic syndrome, General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients, Samsoon, G., *et al.* 653–656
Complications, hypertension, Anaesthetic management of renin secreting nephroblastoma, Charlton, G. A., *et al.* 206–209
——, Preoperative silent ischaemia is related to hypertension, Muir, A. D., *et al.*, (*ARS*) 540P
——, Verapamil and cardiovascular responses to tracheal intubation, Nishikawa, T., (*C*) 225
——, Verapamil and cardiovascular responses to tracheal intubation, Yaku, H., *et al.*, (*C*) 225–226
Complications, hypotension, Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section, Wennberg, E., *et al.* 13–18
Complications, hypoxaemia, Video surveillance of oxygen administration by mask in postoperative patients, Nolan, K. M., *et al.* 194–196
Complications, myalgia, The importance of activity and pretreatment in the prevention of suxamethonium myalgias, Oxorn, D. C., *et al.* 200–201
Complications, myasthenia gravis, Onset of neuromuscular block in myasthenic patients, Baraka, A., (*C*) 227–228
Complications, myocardial infarction, Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery, Stühmeier, K. D., *et al.* 602–606
Complications, osteogenesis imperfecta, Antenatal assessment for anaesthesia, Cody, M. W., *et al.*, (*C*) 332
Complications, overdose, Overdose of opioid from patient-controlled analgesia pumps, Notcutt, W. G., *et al.* 95–97
Complications, pacemaker failure, Apparent pacemaker failure caused by activation of ventricular threshold test by a magnetic instrument mat during general anaesthesia, Purday, J. P., *et al.* 645–646
Complications, pruritus, Intrathecal diamorphine–bupivacaine during labour, Kestin, I. G., (*C*) 108
——, Intrathecal diamorphine–bupivacaine during labour, Scott, P. V., *et al.*, (*C*) 108
Complications, regurgitation, Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, Barker, P., *et al.* 314–315
Complications, respiratory depression, General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients, Samsoon, G., *et al.* 653–656
——, Life-threatening acute respiratory distress in late pregnancy, Mettam, I. M., *et al.* 420–421
——, Overdose of opioid from patient-controlled analgesia pumps, Notcutt, W. G., *et al.* 95–97
——, Respiratory depression after extradural fentanyl, Wang, C. Y., (*C*) 544
Complications, septicaemia, Delayed septicaemia after extradural steroid treatment, Elliott, R. H., *et al.*, (*C*) 422

——, Delayed septicaemia after extradural steroid treatment, Scriven, M. W., *et al.*, (*C*) 422–423

Complications, skin injury, thermal, Skin injury in an infant with pulse oximetry, Pettersen, B., *et al.* 204–205

——, Skin injury with a pulse oximeter, Bethune, D. W., *et al.*, (*C*) 665

——, Skin injury with a pulse oximeter, Pettersen, B., *et al.*, (*C*) 665

Complications, thrombosis, Perioperative blood loss and its reduction: the role of the anaesthetist, Simpson, P. 498–507

——, Venous sequelae of diclofenac, Berry, C. B., *et al.*, (*C*) 332

Complications, tracheal compression, Fatal tracheal compression after haemorrhage into the axilla, Cook, L. B., *et al.* 322–324

Complications, uraemia, Propofol in uraemic patients, Lewis, I. H., *et al.*, (*C*) 329

Complications, uterine rupture, Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine, Tehan, B. 520–521

Critical Care Toxicology (*Contemporary Management in Critical Care* series), Hoffman, R. S., *et al.*, (editors), (*R*) 547

Diabetes, Effect of diabetic autonomic dysfunction on the cardiovascular responses to induction of anaesthesia and tracheal intubation, Vohra, A., *et al.*, (*ARS*) 212–213P

Dog, Effect of graded infusion rates of propofol on regional and global left ventricular function in the dog, Puttick, R. M., *et al.* 375–381

——, Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs, Finegan, B. A., *et al.* 492–497

——, Halothane produces potent endothelium-independent vasodilatation in canine middle cerebral arteries, Flynn, N. M., *et al.*, (*ARS*) 210P

Dripps/Eckenhoff/Vandam Introduction to Anaesthesia, 8th Edn, Longnecker, D. E., *et al.*, (editors), (*R*) 231

Drug delivery, injection speed, Effect of speed of injection of 0.5% plain bupivacaine on the spread of spinal anaesthesia, Tuominen, M., *et al.* 148–149

Drug Infusions in Anesthesiology, Fragen, R. J., (editor), (*R*) 112

Education, The United Kingdom as seen by a Japanese Anaesthetist, Mizushima, A., (*C*) 108–109

Education, junior staff, Training in fibreoptic intubation, Peskett, M. J., (*C*) 331

——, Training in fibreoptic tracheal intubation in the North of England, Wood, P. R., *et al.* 202–203

Ehlers-Danlos syndrome, Anaesthesia for Caesarean section in a patient with Ehlers-Danlos syndrome type IV, Brighouse, D., *et al.* 517–519

Emergency Medicine and the Anaesthetist (*Baillière's Clinical Anaesthesiology* series), Delooz, H. H., (editor), (*R*) 546

Enzymes, cholinesterase, Pharmacodynamics of mivacurium chloride in the cirrhotic patient, Devlin, J. C., *et al.*, (*ARS*) 534–535P

——, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585

Enzymes, methionine synthase, Influence of vitamin B_{12} status on the inactivation of methionine synthase by nitrous oxide, Landon, M. J., *et al.* 81–86

Enzymes, tryptase, Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs, Laroche, D., *et al.* 611–614

Epilepsy, Propofol anticonvulsant activity in experimental epileptic status, De Riu, P. L., *et al.* 177–181

Equipment, airway, A new look at the breath of life, Ward, M. E., (*E*) 339–340

——, A new technique for two-hand bag valve mask ventilation, Thomas, A. N., *et al.* 397–398

——, Comparison of nasal cannula and face mask for oxygen administration in postoperative patients, Nolan, K. M., *et al.*, (*ARS*) 214–215P

——, Comparison of the use of the laryngeal mask and face mask by inexperienced personnel, Tolley, P. M., *et al.* 320–321

——, Cricoid pressure may prevent insertion of the laryngeal mask airway, Ansermino, J. M., *et al.* 465–467

——, Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia, Rabey, P. G., *et al.* 346–348

——, Gastric regurgitation during general anaesthesia in the supine position with the laryngeal and face mask airways, El Mikatti, N., *et al.*, (*ARS*) 529–530P

——, Hypoxaemia and insertion of the laryngeal mask airway, Gillies, G. W. A., (*C*) 661

——, Hypoxaemia and insertion of the laryngeal mask airway, Yaddanapudi, L. N., *et al.*, (*C*) 661

——, Laryngeal mask airway: a more successful method of insertion, Matta, B., *et al.*, (*ARS*) 215P

——, Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, Barker, P., *et al.* 314–315

——, The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses, Lamb, K., *et al.* 143–147

——, Video surveillance of oxygen administration by mask in postoperative patients, Nolan, K. M., *et al.* 194–196

Equipment, anaesthesia machines, Where is the bobbin? Bras, P., *et al.*, (*ARS*) 539P

Equipment, anaesthetic analysers, Bedside respiratory measurements with the Siemens-Elema CO_2 Analyzer, Fletcher, R., (*C*) 227

——, Bedside respiratory measurements with the Siemens-Elema CO_2 Analyzer, Puri, G. D., *et al.*, (*C*) 227

Equipment, breathing systems, Breakdown of halogenated inhalation anaesthetic agents with water vapour in breathing systems, Beatty, P. C. W., *et al.*, (*ARS*) 216P

——, Control of carbon dioxide in circle systems, McHale, S. P., *et al.*, (*ARS*) 529P

——, Damage to coaxial breathing systems, Liddle, M. W. D., (*C*) 425

——, Damage to coaxial breathing systems, Williams, A. R., (*C*) 425

——, Describing circle systems, Wolff, A. H., *et al.*, (*ARS*) 539P

——, Determination of the onset of rebreathing: comparison of six methods during spontaneous ventilation, Barrie, J. R., *et al.*, (*ARS*) 527P

——, European Standardization Committee on Anaesthetic Equipment, Zbinden, A. M., (*C*) 543

——, Fractional delivery of fresh gas: a new index of the efficiency of semi-closed breathing systems, Beatty, P. C. W., *et al.* 474–477

——, Mouth mask ventilation: use of a Pall Ultipor breathing system and effect of mask design, Thomas, A. N., *et al.*, (*ARS*) 527–528P

——, Oxygen uptake during rebreathing in a Mapleson A system, Campkin, N., *et al.*, (*ARS*) 538P

——, Parallel Lack breathing system: fresh gas flow requirements during spontaneous ventilation, Ooi, R., *et al.*, (*ARS*) 216P

——, Rebreathing in the Magill breathing system, Soni, N., *et al.*, (*ARS*) 215–216P

Equipment, cannulae nasal, Comparison of nasal cannula and face mask for oxygen administration in postoperative patients, Nolan, K. M., *et al.*, (*ARS*) 214–215P

——, Use of nasal oxygen cannulae to monitor postoperative breathing, Nimmo, A. F., *et al.*, (*ARS*) 539–540P

Equipment, catheter guides, Retrograde intubation—a facilitated approach, Dhara, S. S. 631–633

Equipment, catheters subarachnoid, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.* 634–636

——, Continuous subarachnoid infusion of local anaesthetic, Morton, C. P. J., *et al.*, (*ARS*) 533P

Equipment, catheters suction, Use of suction catheters as an alternative to tracheal tubes in adults, Gataure, P. S., *et al.* 657–658

Equipment, collars, Effect of a cervical collar on the tidal volume of anaesthetized adult patients, Dodd, F. M., *et al.*, (*ARS*) 526–527P

Equipment, computers, Continuous collection of pulse oximetry data: a new, inexpensive, portable computerized method, Ronald, A. L., *et al.* 105–107

——, Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma, Chaudhri, S., *et al.* 607–610

Equipment, cuffs tracheal, Tracheal models which simulate the compliance of the adult male trachea, Lomholt, N. 98–100

Equipment, gas analysers, Effect of speed of response of capnographs on the accuracy of measurements during anaesthesia, Willard, T. B., *et al.*, (*ARS*) 213P

Equipment, gas mixers, Oxygen wastage by oxygen-air mixers, Williams, N. J., *et al.*, (*C*) 228

Equipment, heat-moisture exchangers, An active heat and moisture exchanger, Kapadia, F., *et al.* 640–642

——, Bacterial retention properties of heat and moisture exchange filters, Lee, M. G., *et al.* 522–525

Equipment, infusion systems, patient-controlled, Overdose of opioid from patient-controlled analgesia pumps, Notcutt, W. G., *et al.* 95–97

Equipment, magnetic mat, Apparent pacemaker failure caused by activation of ventricular threshold test by a magnetic instrument mat during general anaesthesia, Purday, J. P., *et al.* 645–646

Equipment, masks anaesthesia, Comparison of nasal cannula and face mask for oxygen administration in postoperative patients, Nolan, K. M., *et al.*, (*ARS*) 214–215P

——, Comparison of the use of the laryngeal mask and face mask by inexperienced personnel, Tolley, P. M., *et al.* 320–321

——, Cricoid pressure may prevent insertion of the laryngeal mask airway, Ansermino, J. M., *et al.* 465–467

——, Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia, Rabey, P. G., *et al.* 346–348

——, Gastric regurgitation during general anaesthesia in the supine position with the laryngeal and face mask airways, El Mikatti, N., *et al.*, (*ARS*) 529–530P

——, Hypoxaemia and insertion of the laryngeal mask airway, Gillies, G. W. A., (*C*) 661

——, Hypoxaemia and insertion of the laryngeal mask airway, Yaddanapudi, L. N., *et al.*, (*C*) 661

——, Laryngeal mask airway: a more successful method of insertion, Matta, B., *et al.*, (*ARS*) 215P

——, Mouth mask ventilation: use of a Pall Ultipor breathing system and effect of mask design, Thomas, A. N., *et al.*, (*ARS*) 527–528P

——, Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, Barker, P., *et al.* 314–315

——, The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses, Lamb, K., *et al.* 143–147

——, Video surveillance of oxygen administration by mask in postoperative patients, Nolan, K. M., *et al.* 194–196

Equipment, masks surgical, Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway, Philips, B. J., *et al.* 407–408

ment, mirrors, Use of a dental mirror in simulated
ficult laryngoscopy, Toff, N. J., (*ARS*) 218–219P
Equip nent, needles, Insulated regional block needles, Jones,
dif , (*C*) 423–424
Equipr lated regional block needles, Read, M. S., (*C*) 423
R. F llic fragments and the combined spinal–extradural
——, Insu e, Carrie, L. E. S., (*C*) 662–663
——, Metal ragments and the combined spinal–extradural
technique DOR, J., (*C*) 663
——, Metallic e injury caused by injection needles used
technique, El sia: influence of bevel configuration,
——, Peripheral nerv l, Rice, A. S. C., *et al.* 433–438
in regional anaesth dache in urological surgery: an
studied in a rat mode spinal needle, Harrison,
——, Postdural puncture hea
evaluation of the atraumati
D. A., *et al.*, (*ARS*) 540–541P ion: comparison of
——, Spinal anaesthesia for Caesarean sect es with 26-gauge
22-gauge and 25-gauge Whiteacre needl 594
Quincke needles, Shutt, L. E., *et al.* 589– ion of pulse
Equipment, pulse oximeters, Continuous collec terized
oximetry data: a new, inexpensive, portable compu
method, Ronald, A. L., *et al.* 105–107

——, Skin injury in an infant with pulse oximetry, Pettersen B., *et al.* 204–205

——, Skin injury with a pulse oximeter, Bethune, D. W., *et al.*, (*C*) 665

——, Skin injury with a pulse oximeter, Pettersen, B., *et al.*, (*C*) 665

Equipment, standardization, European Standardization Committee on Anaesthetic Equipment, Zbinden, A. M., (*C*) 543

Equipment, ultrasound machines, The Siterite ultrasound machine: an aid to internal jugular vein cannulation? Armstrong, P. J., *et al.*, (*ARS*) 533–534P

Equipment, ventilators, Oxygen wastage by oxygen–air mixers, Williams, N. J., *et al.*, (*C*) 228

Ethics, Dual publication of abstracts, Campbell, I. T., (*C*) 227

——, Dual publication of abstracts, Smith, G., (*C*) 227

Eye, intraocular melanoma, Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma, Chaudhri, S., *et al.* 607–610

Eye, intraocular pressure, Effect of rocuronium and vecuronium on intraocular pressure, Hull, J. M., *et al.*, (*ARS*) 534P

——, The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses, Lamb, K., *et al.* 143–147

Fetus, Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia, Eddleston, J. M., *et al.* 154–158

——, Elimination of bupivacaine and pethidine from the rabbit feto–placental unit, Carson, R. J., *et al.* 150–153

Fluid balance, Comparison of hypertonic saline (5%), isotonic saline and Ringer's lactate solutions for fluid preloading before lumbar extradural anaesthesia, Veroli, P., *et al.* 461–464

Formulations, diluents, Venous sequelae of diclofenac, Berry, C. B., *et al.*, (*C*) 332

——, Venous sequelae of diclofenac, Gopinath, R., (*C*) 332

Formulations, stability, Pharmacodynamic stability of a mixture of propofol and alfentanil, Taylor, I. N., *et al.* 168–171

Gastrointestinal tract, antacids, Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery, Escolano, F., *et al.* 404–406

Gastrointestinal tract, emptying, A longitudinal study of gastric emptying of a test meal during pregnancy, Magides, A. D., *et al.*, (*ARS*) 529P

——, Effect of four different maintenance anaesthetic techniques for minor surgery on gastric emptying, Bennett, M. W. R., *et al.*, (*ARS*) 220P

Gastrointestinal tract, lower oesophageal sphincter, Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia, Rabey, P. G., *et al.* 346–348

Gastrointestinal tract, oesophageal contractility, Somatic movement and oesophageal motility during isoflurane anaesthesia, Mather, C., *et al.* 40–44

Gastrointestinal tract, pH, Bacterial overgrowth and gastric dysfunction, Inglis, T., (*C*) 545

——, Bacterial overgrowth and gastric dysfunction, Wilder-Smith, C. H., (*C*) 545

——, Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery, Escolano, F., *et al.* 404–406

Gastrointestinal tract, prokinesis, Current management of postoperative nausea and vomiting, Rowbotham, D. J. 46–59S

Gastrointestinal tract, reflux, Bacterial overgrowth and gastric dysfunction, Inglis, T., (*C*) 545

——, Bacterial overgrowth and gastric dysfunction, Wilder-Smith, C. H., (*C*) 545

——, Gastric regurgitation during general anaesthesia in the supine position with the laryngeal and face mask airways, El Mikatti, N., *et al.*, (*ARS*) 529–530P

——, Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, Barker, P., *et al.* 314–315

Gastrointestinal tract, reflux, physiology, Physiology of nausea and vomiting: speculations on the mechanisms of postoperative nausea and vomiting, Andrews, P. L. R. 2–19S

Gastrointestinal tract, volume, Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery, Escolano, F., *et al.* 404–406

Genetic factors, A National Database on hepatitis after exposure to inhaled anaesthetics, Kenna, J. G., *et al.*, (*C*) 228–229

etic factors, hyperthermia, Is muscle biopsy for
Ge lignant hyperthermia diagnosis still necessary? Ball,
ma al., (*ARS*) 222–223P
S. P., *et* **seudocholinesterase,** Factors affecting
Genetic factors, p course of neuromuscular block
magnitude and time nium, Vanlinthout, L. E. H.,
produced by suxametho
et al. 29–35

Guineapig, Comparison of the relaxant effects of diazepam, flunitrazepam and midazolam on airway smooth muscle, Koga, Y., *et al.* 65–69

Heart, arrhythmia, electroversion, Midazolam and cardioversion, Gupta, A., *et al.*, (*C*) 422

Heart, atria, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, Micol, J. A., *et al.* 487–491

Heart block, calcium channel blockers, Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs, Finegan, B. A., *et al.* 492–497

Heart, blood flow, myocardial, Effect of graded infusion rates of propofol on regional and global left ventricular function in the dog, Puttick, R. M., *et al.* 375–381

Heart, cardiac output, Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate, Price, M. L., *et al.* 172–176

——, Influence of cardiac output on the correlation between

mixed venous and central venous oxygen saturation, BERRIDGE, J. C. 409–410
——, Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: comparison with the thermodilution technique, RYAN, T., *et al.* 101–104
Heart, cardiopulmonary bypass, Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome, STEPHAN, H., *et al.* 51–57
——, EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects, LAYCOCK, G. J. A., *et al.* 356–362
——, The role of enoximone in cardiac surgery, BOLDT, J., *et al.* 45–50
Heart, chronotropism, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, MICOL, J. A., *et al.* 487–491
Heart, coronary artery bypass, Auto-PEEP, lung volume and sternotomy, FLETCHER, R., (*ARS*) 527P
——, Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery, LANGE, H., *et al.* 478–481
Heart, coronary occlusion, Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery, STÜHMEIER, K. D., *et al.* 602–606
Heart, dobutamine, Effects of detomidine, dopamine and dobutamine on selected Doppler echocardiographic variables in the horse, YOUNG, L. E., *et al.*, (*ARS*) 222P
Heart, dopamine, Effects of detomidine, dopamine and dobutamine on selected Doppler echocardiographic variables in the horse, YOUNG, L. E., *et al.*, (*ARS*) 222P
Heart, enoximone, The role of enoximone in cardiac surgery, BOLDT, J., *et al.* 45–50
Heart, heart rate, Effect of rocuronium and vecuronium on intraocular pressure, HULL, J. M., *et al.*, (*ARS*) 534P
——, Heart rate spectrum analysis during induction of anaesthesia with thiopentone or propofol, HOWELL, S., *et al.*, (*ARS*) 536P
Heart, ischaemia, Effect of brief hypoxaemia on the resting ECG in patients with exercise-induced cardiac ischaemia, ENTWISTLE, M. D., *et al.*, (*ARS*) 536–537P
——, Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery, STÜHMEIER, K. D., *et al.* 602–606
——, Perioperative continuous monitoring of ST-segment changes in patients undergoing elective Caesarean section, TROTTER, T. N., *et al.* 352–355
——, Preoperative silent ischaemia is related to hypertension, MUIR, A. D., *et al.*, (*ARS*) 540P
Heart, isolated preparation, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, MICOL, J. A., *et al.* 487–491
Heart, myocardial function, Effect of graded infusion rates of propofol on regional and global left ventricular function in the dog, PUTTICK, R. M., *et al.* 375–381
Heart, myocardial preservation technique, Influence of myocardial preservation technique on perioperative neutrophil activity in patients undergoing coronary artery graft surgery, COLUMB, M. O., *et al.*, (*ARS*) 211P
Heart, pacemakers artificial, Apparent pacemaker fail[illegible] caused by activation of ventricular threshold test[illegible] magnetic instrument mat during general an[illegible] PURDAY, J. P., *et al.* 645–646
Heart, resuscitation, Advances in [illegible]cardiopulmonary resuscitation, BASKETT, P. J. F. 182–193
——, Comparison of the use of the laryngeal mask and face mask by inexperienced personnel, TOLLEY, P. M., *et al.* 320–321
Heart, vascular pressures, Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate, PRICE, M. L., *et al.* 172–176
Heart, verapamil, Verapamil and cardiovascular responses to tracheal intubation, NISHIKAWA, T., (*C*) 225
——, Verapamil and cardiovascular responses to tracheal intubation, YAKU, H., *et al.*, (*C*) 225–226
Histamine, Atracurium and histamine, ADT, M., (*C*) 110
——, Atracurium and histamine, SCOTT, R. P. F., (*C*) 110
——, Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs, LAROCHE, D., *et al.* 611–614
——, *In vitro* displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs, WILLIAMS, W. R., *et al.* 508–510
Histamine, cyclizine, Current management of postoperative nausea and vomiting, ROWBOTHAM, D. J. 46–59S
History, anaesthesia, The era of relaxant anaesthesia, UTTING, J. E., (*E*) 551–553
History, curare, The era of relaxant anaesthesia, UTTING, J. E., (*E*) 551–553
Hormones, insulin, Isoflurane inhibits insulin secretion from isolated rat pancreatic islets of Langerhans, DESBOROUGH, J. P., *et al.*, (*ARS*) 532P
Hormones, prostaglandins, Effect of diclofenac on renal function and prostacyclin generation after surgery, POWER, I., *et al.* 451–456
——, *In vitro* displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs, WILLIAMS, W. R., *et al.* 508–510
——, Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin $F_{2\alpha}$ in isolated human pial arteries, REINSTRUP, P., *et al.* 615–620
——, The role of prostaglandins in the control of renal function, HARRIS, K., (*E*) 233–235
Hormones, renin, Anaesthetic management of renin secreting nephroblastoma, CHARLTON, G. A., *et al.* 206–209
Horse, Effects of detomidine, dopamine and dobutamine on selected Doppler echocardiographic variables in the horse, YOUNG, L. E., *et al.*, (*ARS*) 222P
Hyperhidrosis, Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis, JEDEIKIN, R., *et al.* 349–351
Hypnotics benzodiazepine, diazepam, Comparison of the relaxant effects of diazepam, flunitrazepam and midazolam on airway smooth muscle, KOGA, Y., *et al.* 65–69
——, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, MURAYAMA, T., *et al.* 61–64
Hypnotics benzodiazepine, flunitrazepam, Comparison of the relaxant effects of diazepam, flunitrazepam and midazolam on airway smooth muscle, KOGA, Y., *et al.* 65–69
Hypnotics benzodiazepine, midazolam, Comparison of inhibitory effect of propofol, thiopentone and midazo[illegible]
on neutrophil polarization *in vitro* in the presence o[illegible] the
absence of human serum albumin, O'DONNELL, N.[illegible] lam
et al. 70–74
——, Comparison of the relaxant effects of diazepa[illegible] G.,
flunitrazepam and midazolam on airway smoo[illegible]
KOGA, Y., *et al.* 65–69
——, EEG and auditory evoked potential P30[illegible] muscle,
psychometric tests in assessing vigilance[illegible] compared with
benzodiazepine sedation and antagonis[illegible] after
W., *et al.* 75–80
——, Effect of age, sex and anaesthetic[illegible]ism, ENGELHARDT,
pharmacokinetics of atracuri[illegible] technique on the
439–443
——, Effect of ketanseri[illegible]um, PARKER, C. J. R., *et al.*
cerebral oxyge[illegible] on global cerebral blood flow and
isoflurane a[illegible] metabolism during midazolam–fentanyl or
——, Hypno[illegible]anaesthesia, OLSEN, K. S., *et al.* 263–268
mid[illegible]tic and anaesthetic interactions between
[illegible]zolam, propofol and alfentanil, SHORT, T. G., *et al.*
——[illegible]2–167
[illegible], Midazolam and cardioversion, GUPTA, A., *et al.*, (*C*) 422
——, Synergistic interaction between midazolam and propofol, MCCLUNE, S., *et al.* 240–245
Hypnotics, detomidine, Effects of detomidine, dopamine and dobutamine on selected Doppler echocardiographic variables in the horse, YOUNG, L. E., *et al.*, (*ARS*) 222P
Hypoxaemia, Changes in respiratory function after laparoscopic cholecystectomy, MARTIN, C. S., *et al.*, (*ARS*) 526P
——, Effect of brief hypoxaemia on the resting ECG in patients with exercise-induced cardiac ischaemia, ENTWISTLE, M. D., *et al.*, (*ARS*) 536–537P
——, Hypoxaemia and insertion of the laryngeal mask airway, GILLIES, G. W. A., (*C*) 661
——, Hypoxaemia and insertion of the laryngeal mask airway, YADDANAPUDI, L. N., *et al.*, (*C*) 661
——, Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia, MADEJ, T. H., *et al.* 554–557
——, Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia, WHEATLEY, R. G., *et al.* 558–561
——, Prolonged postoperative oxygen therapy, HANNING, C. D., (*E*) 115–116

Immune response, Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin, O'DONNELL, N. G., *et al.* 70–74

Immune response, post-anaesthetic hepatitis, A National Database on hepatitis after exposure to inhaled anaesthetics, Kenna, J. G., *et al.*, (*C*) 228–229
Induction, anaesthesia, Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate, Price, M. L., *et al.* 172–176
——, Effect of diabetic autonomic dysfunction on the cardiovascular responses to induction of anaesthesia and tracheal intubation, Vohra, A., *et al.*, (*ARS*) 212–213P
——, Heart rate spectrum analysis during induction of anaesthesia with thiopentone or propofol, Howell, S., *et al.*, (*ARS*) 536P
——, Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol, Barker, P., *et al.* 23–25
——, Vocal cord movement on induction of anaesthesia, Fink, B. R., (*C*) 661
——, Vocal cord movement on induction of anaesthesia, Langton, J., *et al.*, (*C*) 661–662
Infants, Anaesthetic management of renin secreting nephroblastoma, Charlton, G. A., *et al.* 206–209
——, Skin injury in an infant with pulse oximetry, Pettersen, B., *et al.* 204–205
Infection and the Anaesthetist, Stoutenbeek, C. P., *et al.*, (editors), (*R*) 112–113
Infection, bacterial, Bacterial overgrowth and gastric dysfunction, Inglis, T., (*C*) 545
——, Bacterial overgrowth and gastric dysfunction, Wilder-Smith, C. H., (*C*) 545
——, Bacterial retention properties of heat and moisture exchange filters, Lee, M. G., *et al.* 522–525
——, Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway, Philips, B. J., *et al.* 407–408
Infection, nosocomial, Bacterial overgrowth and gastric dysfunction, Inglis, T., (*C*) 545
——, Bacterial overgrowth and gastric dysfunction, Wilder-Smith, C. H., (*C*) 545
——, Delayed septicaemia after extradural steroid treatment, Elliott, R. H., *et al.*, (*C*) 422
——, Delayed septicaemia after extradural steroid treatment, Scriven, M. W., *et al.*, (*C*) 422–423
——, Extradural abscess complicating extradural anaesthesia for Caesarean section, Ngan Kee, W. D., *et al.* 647–652
——, Steroid therapy and extradural analgesia, Ngan Kee, W. D., (*C*) 423
——, Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway, Philips, B. J., *et al.* 407–408
Infusions, Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure, Putensen, C., *et al.* 513–516
Intensive care, Anaesthesia for critically ill children during magnetic resonance imaging, Tobin, J. R., *et al.* 482–486
——, Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin, O'Donnell, N. G., *et al.* 70–74
Intensive care, analgesia, Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure, Putensen, C., *et al.* 513–516
Intensive care, sedation, Effect of physiotherapy on EEG spectral derivatives in sedated patients in the intensive care unit, Wang, D. Y., *et al.*, (*ARS*) 221–222P
Interactions (drug), Effect of administration of vecuronium on recovery from pancuronium and *vice versa*, Hood, J., *et al.*, (*ARS*) 218P
——, Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs, Finegan, B. A., *et al.* 492–497
——, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64
——, Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil, Short, T. G., *et al.* 162–167
——, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, Micol, J. A., *et al.* 487–491
——, Synergistic interaction between midazolam and propofol, McClune, S., *et al.* 240–245
Intubation nasotracheal, fibreoptic, Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol, Barker, P., *et al.* 23–25
Intubation tracheal, Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium, Cooper, R., *et al.* 269–273
Intubation tracheal, complications, Retrograde intubation using the subcricoid region, Lleu, J. C., *et al.*, (*C*) 542
——, Retrograde intubation using the subcricoid region, Shantha, T. R., (*C*) 542
Intubation tracheal, difficult, Recognition and management of difficult airway problems, Butler, P. J., (*C*) 225
——, Recognition and management of difficult airway problems, Calder, I., (*C*) 224
——, Recognition and management of difficult airway problems, Cobley, M., *et al.*, (*C*) 225
——, Recognition and management of difficult airway problems, Heath, M. L., (*C*) 224–225
——, Retrograde intubation—a facilitated approach, Dhara, S. S. 631–633
——, Use of suction catheters as an alternative to tracheal tubes in adults, Gataure, P. S., *et al.* 657–658
Intubation tracheal, extubation, Cardiovascular responses to tracheal extubation, Dhamee, M. S., *et al.*, (*C*) 229
——, Cardiovascular responses to tracheal extubation, Fell, D., *et al.*, (*C*) 229
Intubation tracheal, responses, Effect of diabetic autonomic dysfunction on the cardiovascular responses to induction of anaesthesia and tracheal intubation, Vohra, A., *et al.*, (*ARS*) 212–213P
——, Verapamil and cardiovascular responses to tracheal intubation, Nishikawa, T., (*C*) 225
——, Verapamil and cardiovascular responses to tracheal intubation, Yaku, H., *et al.*, (*C*) 225–226
Intubation tracheal, technique, Recognition and management of difficult airway problems, Cobley, M., *et al.*, (*C*) 225
——, Recognition and management of difficult airway problems, Heath, M. L., (*C*) 224–225
——, Retrograde intubation using the subcricoid region, Lleu, J. C., *et al.*, (*C*) 542
——, Retrograde intubation—a facilitated approach, Dhara, S. S. 631–633
——, Retrograde intubation using the subcricoid region, Shantha, T. R., (*C*) 542
——, Training in fibreoptic intubation, Peskett, M. J., (*C*) 331
——, Use of a dental mirror in simulated difficult laryngoscopy, Toff, N. J., (*ARS*) 218–219P
——, Use of suction catheters as an alternative to tracheal tubes in adults, Gataure, P. S., *et al.* 657–658
Intubation tracheal, training, Training in fibreoptic intubation, Peskett, M. J., (*C*) 331
——, Training in fibreoptic tracheal intubation in the North of England, Wood, P. R., *et al.* 202–203
Ions, calcium, Effects of halothane on cultured neurones, Winlow, W., *et al.*, (*ARS*) 530–531P
——, Halothane-induced changes in intracellular calcium ion concentration in neurones from *Lymnaea stagnalis*, Hopkins, P. M., *et al.*, (*ARS*) 210–211P
——, Inhibition of sodium–calcium exchange increases skeletal muscle contracture response to halothane, Hopkins, P. M., *et al.*, (*ARS*) 531–532P
Ions, potassium, Fentanyl inhibits evoked $[^3H]$noradrenaline release from human neuroblastoma cells, Atcheson, R., *et al.*, (*ARS*) 531P
——, Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin $F_{2\alpha}$ in isolated human pial arteries, Reinstrup, P., *et al.* 615–620
Ions, sodium, Inhibition of sodium–calcium exchange increases skeletal muscle contracture response to halothane, Hopkins, P. M., *et al.*, (*ARS*) 531–532P
——, Molecular actions of racemic ketamine on human CNS sodium channels, Frenkel, C., *et al.* 292–297

Kidney, failure, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585
——, Propofol in uraemic patients, Lewis, I. H., *et al.*, (*C*) 329
Kidney, function, Effect of diclofenac on renal function and prostacyclin generation after surgery, Power, I., *et al.* 451–456
——, The role of prostaglandins in the control of renal function, Harris, K., (*E*) 233–235
Kidney, lithotripsy, Topical anaesthesia for extracorporeal shock wave lithotripsy, McDonald, P. F., *et al.* 399–400
Kidney, nephroblastoma, Anaesthetic management of renin secreting nephroblastoma, Charlton, G. A., *et al.* 206–209
Kidney, transplantation, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585
Kinetics of Anaesthetic Drugs in Clinical Anesthesiology, White, P. F., (editor), (*R*) 667

Larynx, cricoid pressure, Cricoid pressure may prevent insertion of the laryngeal mask airway, Ansermino, J. M., *et al.* 465–467

Larynx, laryngoscopy, Use of a dental mirror in simulated difficult laryngoscopy, Toff, N. J., (*ARS*) 218–219P

Larynx, vocal cords, Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol, Barker, P., *et al.* 23–25

——, Vocal cord movement on induction of anaesthesia, Fink, B. R., (*C*) 661

——, Vocal cord movement on induction of anaesthesia, Langton, J., *et al.*, (*C*) 661–662

Lecture Notes on Anaesthetics, 4th Edn, Lunn, J. N., (*R*) 113

Liver, blood flow, Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery, Lange, H., *et al.* 478–481

——, Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol, Murray, J. M., *et al.* 643–644

Liver, cirrhosis, Pharmacodynamics of mivacurium chloride in the cirrhotic patient, Devlin, J. C., *et al.*, (*ARS*) 534–535P

Liver, disease, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585

Liver, function, Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol, Murray, J. M., *et al.* 643–644

Liver, hepatitis, A National Database on hepatitis after exposure to inhaled anaesthetics, Kenna, J. G., *et al.*, (*C*) 228–229

Liver, hepatotoxicity, Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver, Reckendorfer, H., *et al.* 288–291

Liver, metabolism, Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery, Lange, H., *et al.* 478–481

Liver, transplantation, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585

Lung, function, Changes in respiratory function after laparoscopic cholecystectomy, Martin, C. S., *et al.*, (*ARS*) 526P

——, Determination of the onset of rebreathing: comparison of six methods during spontaneous ventilation, Barrie, J. R., *et al.*, (*ARS*) 527P

——, Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy, Welte, M., *et al.* 637–639

——, Lung function after vecuronium pretreatment in young, healthy patients, Mahajan, R. P., *et al.* 318–319

——, Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy, Joris, J., *et al.* 341–345

Lung, respiratory resistance, Effect of fentanyl on ventilatory resistances during barbiturate general anaesthesia, Cohendy, R., *et al.* 595–598

Lung, tidal volume, Effect of a cervical collar on the tidal volume of anaesthetized adult patients, Dodd, F. M., *et al.*, (*ARS*) 526–527P

Lung, volume, Auto-PEEP, lung volume and sternotomy, Fletcher, R., (*ARS*) 527P

Malignant hyperthermia, Evaluation of spin resonance spectroscopy of red blood cell membranes to detect malignant hyperthermia susceptibility, Halsall, P. J., *et al.* 471–473

——, *In vitro* diagnosis of malignant hyperthermia: influence of electrical stimulation on the contracture response to caffeine, Heytens, L., *et al.* 87–91

——, Inhibition of sodium–calcium exchange increases skeletal muscle contracture response to halothane, Hopkins, P. M., *et al.*, (*ARS*) 531–532P

——, Is muscle biopsy for malignant hyperthermia diagnosis still necessary? Ball, S. P., *et al.*, (*ARS*) 222–223P

——, Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? Ellis, F. R., *et al.* 468–470

Manual of Obstetric Anesthesia, 2nd Edn, Ostheimer, G. W., (editor), (*R*) 547–548

Manual of Post-Anesthesia Care, Jacobsen, W. K., *et al.*, (editors), (*R*) 333–334

Maternal Mortality—The Way Forward. Some Implications of the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–87, Patel, N., (editor), (*R*) 547

MCQ Companion to the Textbook of Anaesthesia, Fell, D., *et al.*, (*R*) 667–668

MCQ for the Higher Examinations in Clinical Pharmacology, McCarthy, G., *et al.*, (*R*) 546

Measurement techniques, carbon dioxide, Bedside respiratory measurements with the Siemens–Elema CO_2 Analyzer, Fletcher, R., (*C*) 227

——, Bedside respiratory measurements with the Siemens–Elema CO_2 Analyzer, Puri, G. D., *et al.*, (*C*) 227

——, Effect of speed of response of capnographs on the accuracy of measurements during anaesthesia, Willard, T. B., *et al.*, (*ARS*) 213P

——, Fractional delivery of fresh gas: a new index of the efficiency of semi-closed breathing systems, Beatty, P. C. W., *et al.* 474–477

Measurement techniques, chemoluminescence, Influence of myocardial preservation technique on perioperative neutrophil activity in patients undergoing coronary artery graft surgery, Columb, M. O., *et al.*, (*ARS*) 211P

Measurement techniques, coagulation, Bleeding time, Bromage, P. R., (*C*) 330

——, Bleeding time, McDonald, R., (*C*) 329

——, Bleeding time, O'Kelly, S. W., *et al.*, (*C*) 330–331

——, Bleeding time, Power, I., (*C*) 329–330

Measurement techniques, contracture test for MH, *In vitro* diagnosis of malignant hyperthermia: influence of electrical stimulation on the contracture response to caffeine, Heytens, L., *et al.* 87–91

——, Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? Ellis, F. R., *et al.* 468–470

Measurement techniques, Doppler echocardiography, Effects of detomidine, dopamine and dobutamine on selected Doppler echocardiographic variables in the horse, Young, L. E., *et al.*, (*ARS*) 222P

Measurement techniques, Doppler ultrasound, Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate, Price, M. L., *et al.* 172–176

——, Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: comparison with the thermodilution technique, Ryan, T., *et al.* 101–104

Measurement techniques, electrodes, impedance, Effects of skin blood flow and temperature on skin–electrode impedance and offset potential, Smith, D. C., (*ARS*) 223P

——, Influence of temperature and posture changes on evoked electromyography, Smith, D. C., *et al.*, (*ARS*) 223P

——, Recording electrode impedance has no effect on evoked EMG responses, Smith, D. C., (*ARS*) 535–536P

Measurement techniques, electromyography, Effects of skin blood flow and temperature on skin–electrode impedance and offset potential, Smith, D. C., (*ARS*) 223P

——, Influence of temperature and posture changes on evoked electromyography, Smith, D. C., *et al.*, (*ARS*) 223P

——, Recording electrode impedance has no effect on evoked EMG responses, Smith, D. C., (*ARS*) 535–536P

Measurement techniques, electron spin resonance, Evaluation of spin resonance spectroscopy of red blood cell membranes to detect malignant hyperthermia susceptibility, Halsall, P. J., *et al.* 471–473

Measurement techniques, nuclear magnetic resonance, Anaesthesia for critically ill children during magnetic resonance imaging, Tobin, J. R., *et al.* 482–486

Measurement techniques, radioimmunoassay, Radioimmunoassay tests and anaphylaxis, Imray, I. McG., *et al.*, (*C*) 543–544

Measurement techniques, spectral analysis, Effect of physiotherapy on EEG spectral derivatives in sedated patients in the intensive care unit, Wang, D. Y., *et al.*, (*ARS*) 221–222P

——, Heart rate spectrum analysis during induction of anaesthesia with thiopentone or propofol, Howell, S., *et al.*, (*ARS*) 536P

Measurement techniques, thermodilution, Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: comparison with the thermodilution technique, Ryan, T., *et al.* 101–104

Measurement techniques, thrombelastography, Thrombelastography, Mallett, S. V., *et al.* 307–313

——, Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects, Orlikowski, C. E. P., *et al.* 159–161

Measurement techniques, tomography, Accidental subdural catheterization: radiological evidence of a possible mechanism for spinal cord damage, McMenemin, I. M., *et al.* 417–419

Mechanical Ventilation and Assisted Respiration, Grenvik, A., *et al.*, (editors), (*R*) 334
Memory, EEG and memory effects of low-dose infusions of propofol, Veselis, R. A., *et al.* 246–254
——, Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion, Bethune, D. W., *et al.* 197–199
Metabolism, free radicals, Effect of propofol and thiopentone on free radical-induced haemolysis, Murphy, P. G., *et al.*, (*ARS*) 532–533P
——, Plasma antioxidant activity in stored blood, Myers, D. S., *et al.*, (*ARS*) 222P
Metabolism, metabolites, Probable resistance to vecuronium involving the 17-hydroxy metabolite, Cozanitis, D. A., (*C*) 110–111
Metabolism, protein, acute phase, Interleukin-6 and the metabolic response to surgery, Hall, G. M., *et al.*, (*E*) 337–338
——, Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy, Joris, J., *et al.* 341–345
Model, mathematical, A logistic regression model for risk stratification of fixed patient factors for postoperative emesis, Palazzo, M. G. A., *et al.*, (*ARS*) 530P
Model, mollusc, Effects of halothane on cultured neurones, Winlow, W., *et al.*, (*ARS*) 530–531P
Model, pig, Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood–brain barrier, Werba, A., *et al.* 382–386
Model, rat, Effects of halothane on cultured neurones, Winlow, W., *et al.*, (*ARS*) 530–531P
——, Peripheral nerve injury caused by injection needles used in regional anaesthesia: influence of bevel configuration, studied in a rat model, Rice, A. S. C., *et al.* 433–438
Model, trachea, Tracheal models which simulate the compliance of the adult male trachea, Lomholt, N. 98–100
Mollusc, Effects of halothane on cultured neurones, Winlow, W., *et al.*, (*ARS*) 530–531P
——, Halothane-induced changes in intracellular calcium ion concentration in neurones from *Lymnaea stagnalis*, Hopkins, P. M., *et al.*, (*ARS*) 210–211P
Monitoring, computerized, Continuous collection of pulse oximetry data: a new, inexpensive, portable computerized method, Ronald, A. L., *et al.* 105–107
Monitoring, depth of anaesthesia, Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane, Newton, D. E. F., *et al.* 122–129
——, Coherence in the auditory evoked response as a measure of arousal during anaesthesia, Sapsford, D. J., *et al.*, (*ARS*) 538P
Monitoring, echocardiography, Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: comparison with the thermodilution technique, Ryan, T., *et al.* 101–104
Monitoring, electrocardiography, Effect of brief hypoxaemia on the resting ECG in patients with exercise-induced cardiac ischaemia, Entwistle, M. D., *et al.*, (*ARS*) 536–537P
——, Perioperative continuous monitoring of ST-segment changes in patients undergoing elective Caesarean section, Trotter, T. N., *et al.* 352–355
Monitoring, electroencephalography, EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism, Engelhardt, W., *et al.* 75–80
——, EEG and memory effects of low-dose infusions of propofol, Veselis, R. A., *et al.* 246–254
——, EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects, Laycock, G. J. A., *et al.* 356–362
——, Effect of physiotherapy on EEG spectral derivatives in sedated patients in the intensive care unit, Wang, D. Y., *et al.*, (*ARS*) 221–222P
Monitoring, evoked potentials, A method to facilitate regional anaesthesia by detection of mixed nerve action potentials, Wee, M. Y. K., *et al.* 411–413
——, Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane, Newton, D. E. F., *et al.* 122–129
——, Coherence in the auditory evoked response as a measure of arousal during anaesthesia, Sapsford, D. J., *et al.*, (*ARS*) 538P
——, EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism, Engelhardt, W., *et al.* 75–80
——, Effects of isoflurane anaesthesia on the median nerve somatosensory evoked potential in children, Mason, D. G., *et al.* 562–566
——, Recording electrode impedance has no effect on evoked EMG responses, Smith, D. C., (*ARS*) 535–536P
——, Sequential measurement of the median nerve somatosensory evoked potential during isoflurane anaesthesia in children, Mason, D. G., *et al.* 567–569
——, Some effects of isoflurane on I waves of the motor evoked potential, Hicks, R. G., *et al.* 130–136
Monitoring, intensive care, Anaesthesia for critically ill children during magnetic resonance imaging, Tobin, J. R., *et al.* 482–486
Monitoring, oxygen, Continuous collection of pulse oximetry data: a new, inexpensive, portable computerized method, Ronald, A. L., *et al.* 105–107
——, Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation, Berridge, J. C. 409–410
——, Inspiratory to end-tidal oxygen difference, Bengtson, J. P., *et al.*, (*C*) 663
——, Inspiratory to end-tidal oxygen difference, Schrader, M., (*C*) 663
——, Skin injury in an infant with pulse oximetry, Pettersen, B., *et al.* 204–205
——, Video surveillance of oxygen administration by mask in postoperative patients, Nolan, K. M., *et al.* 194–196
Monitoring, ultrasound, The Siterite ultrasound machine: an aid to internal jugular vein cannulation? Armstrong, P. J., *et al.*, (*ARS*) 533–534P
Monitoring, ventilation, Use of nasal oxygen cannulae to monitor postoperative breathing, Nimmo, A. F., *et al.*, (*ARS*) 539–540P
Muscle respiratory, function, Comparison of the relaxant effects of diazepam, flunitrazepam and midazolam on airway smooth muscle, Koga, Y., *et al.* 65–69
——, Sternocleidomastoid muscle contractility at different levels of isoflurane anaesthesia in humans, Oshima, T., *et al.* 236–239
Muscle skeletal, Action of ketamine on isolated porcine trachealis muscle, Hatch, D. J., *et al.*, (*ARS*) 217P
——, Comparison of atracurium-induced neuromuscular block in rectus abdominis and hand muscles of man, Saddler, J. M., *et al.* 26–28
Muscle skeletal, blood flow, Etomidate shortens the onset time of neuromuscular block, Gill, R. S., *et al.* 444–446
Muscle skeletal, contractility, Inhibition of sodium–calcium exchange increases skeletal muscle contracture response to halothane, Hopkins, P. M., *et al.*, (*ARS*) 531–532P
——, Is muscle biopsy for malignant hyperthermia diagnosis still necessary? Ball, S. P., *et al.*, (*ARS*) 222–223P
——, Sternocleidomastoid muscle contractility at different levels of isoflurane anaesthesia in humans, Oshima, T., *et al.* 236–239
Muscle skeletal, diaphragm, Relative pre- and postjunctional effects of a new vecuronium analogue, Org 9426, at the rat neuromuscular junction, Tian, L., *et al.* 284–287
Muscle skeletal, responses, Somatic movement and oesophageal motility during isoflurane anaesthesia, Mather, C., *et al.* 40–44
Muscle vascular, pharmacology, Halothane produces potent endothelium-independent vasodilatation in canine middle cerebral arteries, Flynn, N. M., *et al.*, (*ARS*) 210P
Muscle vascular, responses, Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin $F_{2\alpha}$ in isolated human pial arteries, Reinstrup, P., *et al.* 615–620
Myasthenia gravis, Onset of neuromuscular block in myasthenic patients, Baraka, A., (*C*) 227–228

Nerve, damage (postoperative), Peripheral nerve damage and regional anaesthesia, Chambers, W. A., (*E*) 429–430
——, Peripheral nerve injury caused by injection needles used in regional anaesthesia: influence of bevel configuration, studied in a rat model, Rice, A. S. C., *et al.* 433–438
Nerve, potential, Effects of halothane on cultured neurones, Winlow, W., *et al.*, (*ARS*) 530–531P
Nerve, synaptosome, Effect of halothane on $[^3H]$methylcholine uptake into rat brain synaptosomes, Griffiths, R., *et al.*, (*ARS*) 530P
Nerve, transmission, Effect of halothane on $[^3H]$methylcholine uptake into rat brain synaptosomes, Griffiths, R., *et al.*, (*ARS*) 530P
Nerve–muscle preparations, Relative pre- and postjunctional effects of a new vecuronium analogue, Org 9426, at the rat neuromuscular junction, Tian, L., *et al.* 284–287

Neuromuscular block, allergy, Anaphylactoid or carcinoid? Batchelor, A. M., *et al.* 325–327
——, Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs, Laroche, D., *et al.* 611–614
——, *In vitro* displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs, Williams, W. R., *et al.* 508–510
Neuromuscular block, antagonism, Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly, McCarthy, G. J., *et al.* 281–283
Neuromuscular block, atracurium, Atracurium and histamine, Adt, M., (*C*) 110
——, Atracurium and histamine, Scott, R. P. F., (*C*) 110
——, Comparison of atracurium-induced neuromuscular block in rectus abdominis and hand muscles of man, Saddler, J. M., *et al.* 26–28
——, Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium, Parker, C. J. R., *et al.* 439–443
——, Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver, Reckendorfer, H., *et al.* 288–291
——, Influence of body weight and gender on the pharmacodynamics of atracurium, Devlin, J. C., *et al.*, (*ARS*) 217–218P
——, Relationship of the train-of-four ratio to plasma atracurium concentration, Parker, C. J. R., *et al.* 274–280
——, The importance of activity and pretreatment in the prevention of suxamethonium myalgias, Oxorn, D. C., *et al.* 200–201
Neuromuscular block, laudanosine, Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver, Reckendorfer, H., *et al.* 288–291
Neuromuscular block, measurement of response, Effects of skin blood flow and temperature on skin–electrode impedance and offset potential, Smith, D. C., (*ARS*) 223P
——, Factors affecting magnitude and time course of neuromuscular block produced by suxamethonium, Vanlinthout, L. E. H., *et al.* 29–35
——, Fade during recovery from vecuronium, Campkin, N. T. A., *et al.*, (*C*) 226–227
——, Influence of temperature and posture changes on evoked electromyography, Smith, D. C., *et al.*, (*ARS*) 223P
——, Relationship of the train-of-four ratio to plasma atracurium concentration, Parker, C. J. R., *et al.* 274–280
Neuromuscular block, mivacurium, Pharmacodynamics of mivacurium chloride in the cirrhotic patient, Devlin, J. C., *et al.*, (*ARS*) 534–535P
——, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585
Neuromuscular block, pancuronium, Comparison of recovery index of Org 9426 with simultaneous administration of pancuronium in the isolated arm compared with vecuronium and pancuronium, Fawcett, W., *et al.*, (*ARS*) 218P
——, Effect of administration of vecuronium on recovery from pancuronium and *vice versa*, Hood, J., *et al.*, (*ARS*) 218P
——, Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood–brain barrier,. Werba, A., *et al.* 382–386
Neuromuscular block, priming, Lung function after vecuronium pretreatment in young, healthy patients, Mahajan, R. P., *et al.* 318–319
Neuromuscular block, recovery, Comparison of atracurium-induced neuromuscular block in rectus abdominis and hand muscles of man, Saddler, J. M., *et al.* 26–28
——, Comparison of recovery index of Org 9426 with simultaneous administration of pancuronium in the isolated arm compared with vecuronium and pancuronium, Fawcett, W., *et al.*, (*ARS*) 218P
——, Effect of administration of vecuronium on recovery from pancuronium and *vice versa*, Hood, J., *et al.*, (*ARS*) 218P
——, Influence of circulating drug on recovery of neuromuscular block in the isolated forearm, Hood, J. R., *et al.*, (*ARS*) 535P
——, Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia, Mayer, M., *et al.* 511–512
——, Recording electrode impedance has no effect on evoked EMG responses, Smith, D. C., (*ARS*) 535–536P
Neuromuscular block, resistance, Probable resistance to vecuronium involving the 17-hydroxy metabolite, Cozanitis, D. A., (*C*) 110–111
——, Repeated resistance to non-depolarizing neuromuscular blocking drugs in a patient with multiple myeloma, Ip Yam, C., *et al.*, (*C*) 111
Neuromuscular block, rocuronium, Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium, Cooper, R., *et al.* 269–273
——, Comparison of recovery index of Org 9426 with simultaneous administration of pancuronium in the isolated arm compared with vecuronium and pancuronium, Fawcett, W., *et al.*, (*ARS*) 218P
——, Effect of rocuronium and vecuronium on intraocular pressure, Hull, J. M., *et al.*, (*ARS*) 534P
——, Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia, Mayer, M., *et al.* 511–512
——, Relative pre- and postjunctional effects of a new vecuronium analogue, Org 9426, at the rat neuromuscular junction, Tian, L., *et al.* 284–287
Neuromuscular block, suxamethonium, Anaphylactoid or carcinoid? Batchelor, A. M., *et al.* 325–327
——, Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium, Cooper, R., *et al.* 269–273
——, Factors affecting magnitude and time course of neuromuscular block produced by suxamethonium, Vanlinthout, L. E. H., *et al.* 29–35
——, Onset of neuromuscular block in myasthenic patients, Baraka, A., (*C*) 227–228
——, The importance of activity and pretreatment in the prevention of suxamethonium myalgias, Oxorn, D. C., *et al.* 200–201
Neuromuscular block, vecuronium, Comparison of recovery index of Org 9426 with simultaneous administration of pancuronium in the isolated arm compared with vecuronium and pancuronium, Fawcett, W., *et al.*, (*ARS*) 218P
——, Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly, McCarthy, G. J., *et al.* 281–283
——, Effect of administration of vecuronium on recovery from pancuronium and *vice versa*, Hood, J., *et al.*, (*ARS*) 218P
——, Effect of rocuronium and vecuronium on intraocular pressure, Hull, J. M., *et al.*, (*ARS*) 534P
——, Etomidate shortens the onset time of neuromuscular block, Gill, R. S., *et al.* 444–446
——, Fade during recovery from vecuronium, Campkin, N. T. A., *et al.*, (*C*) 226–227
——, Influence of circulating drug on recovery of neuromuscular block in the isolated forearm, Hood, J. R., *et al.*, (*ARS*) 535P
——, Lung function after vecuronium pretreatment in young, healthy patients, Mahajan, R. P., *et al.* 318–319
——, Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia, Mayer, M., *et al.* 511–512
——, Onset of neuromuscular block in myasthenic patients, Baraka, A., (*C*) 227–228
——, Probable resistance to vecuronium involving the 17-hydroxy metabolite, Cozanitis, D. A., (*C*) 110–111
Neuromuscular function, synapses, Relative pre- and postjunctional effects of a new vecuronium analogue, Org 9426, at the rat neuromuscular junction, Tian, L., *et al.* 284–287
Neuromuscular transmission, Relationship of the train-of-four ratio to plasma atracurium concentration, Parker, C. J. R., *et al.* 274–280
Non-steroidal anti-inflammatory drugs, Effect of diclofenac on renal function and prostacyclin generation after surgery, Power, I., *et al.* 451–456
——, Ketorolac trometamol for postoperative analgesia after orthopaedic surgery, Kinsella, J., *et al.* 19–22
——, Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy, Merry, A. F., *et al.* 92–94

Organizations, European Standardization Committee, European Standardization Committee on Anaesthetic Equipment, Zbinden, A. M., (*C*) 543
Organizations, Japanese Society of Anesthesiology, The United Kingdom as seen by a Japanese Anaesthetist, Mizushima, A., (*C*) 108–109
Organizations, Medical Research Council, Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), Macdonald, R., (*C*) 109–110
——, Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), de Swiet, M., *et al.*, (*C*) 109

Osteogenesis imperfecta, Antenatal assessment for anaesthesia, Cody, M. W., *et al.*, (*C*) 332

Oxygen, delivery systems, Oxygen wastage by oxygen–air mixers, Williams, N. J., *et al.*, (*C*) 228

Oxygen, gradients, Derivation of $\dot{V}/\dot{Q}$ from the position of the $P\text{I}_{O_2}$ *vs* $S\text{p}_{O_2}$ curve, Sapsford, D. J., *et al.*, (*ARS*) 541P

Oxygen, inspired concentration, Derivation of $\dot{V}/\dot{Q}$ from the position of the $P\text{I}_{O_2}$ *vs* $S\text{p}_{O_2}$ curve, Sapsford, D. J., *et al.*, (*ARS*) 541P

Oxygen, saturation, Comparison of nasal cannula and face mask for oxygen administration in postoperative patients, Nolan, K. M., *et al.*, (*ARS*) 214–215P

——, Continuous collection of pulse oximetry data: a new, inexpensive, portable computerized method, Ronald, A. L., *et al.* 105–107

——, Derivation of $\dot{V}/\dot{Q}$ from the position of the $P\text{I}_{O_2}$ *vs* $S\text{p}_{O_2}$ curve, Sapsford, D. J., *et al.*, (*ARS*) 541P

——, Effect of brief hypoxaemia on the resting ECG in patients with exercise-induced cardiac ischaemia, Entwistle, M. D., *et al.*, (*ARS*) 536–537P

——, Hypoxaemia and insertion of the laryngeal mask airway, Gillies, G. W. A., (*C*) 661

——, Hypoxaemia and insertion of the laryngeal mask airway, Yaddanapudi, L. N., *et al.*, (*C*) 661

——, Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation, Berridge, J. C. 409–410

——, Postoperative oxygenation in the elderly after ophthalmic surgery: comparison of local and general anaesthesia, McCarthy, G., *et al.*, (*ARS*) 213–214P

——, Risk factors for oxygen desaturation during sleep, after abdominal surgery, Beydon, L., *et al.* 137–142

Oxygen, therapy, Comparison of nasal cannula and face mask for oxygen administration in postoperative patients, Nolan, K. M., *et al.*, (*ARS*) 214–215P

——, Prolonged postoperative oxygen therapy, Hanning, C. D., (*E*) 115–116

——, Video surveillance of oxygen administration by mask in postoperative patients, Nolan, K. M., *et al.* 194–196

Oxygen, transport, Effect of dobutamine on oxygen supply and uptake in healthy volunteers, Bhatt, S. B., *et al.* 298–303

Oxygen, uptake, Oxygen uptake during rebreathing in a Mapleson A system, Campkin, N., *et al.*, (*ARS*) 538P

Pain, cannulation, Pressor response to venous cannulation and effect of local anaesthetic infiltration, Langham, B. T., *et al.*, (*ARS*) 537–538P

Pain, injection, Pain on the injection of propofol: comparison of lignocaine with metoclopramide, Ganta, R., *et al.* 316–317

Pain, mechanism, Pre-emptive analgesia, McQuay, H. J., (*E*) 1–3

Pain, pathological, Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine, Tehan, B. 520–521

Pain, postoperative, Anaesthetic factors contributing to postoperative nausea and vomiting, Rabey, P. G., *et al.* 40–45S

——, Comparison of extradural administration of sufentanil, morphine and sufentanil–morphine combination after Caesarean section, Dottrens, M., *et al.* 9–12

——, Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy, Welte, M., *et al.* 637–639

——, Effect of preoperative opioid administration on postoperative pain, Dahl, J. B., *et al.*, (*C*) 424–425

——, Effect of preoperative opioid administration on postoperative pain, Katz, J., *et al.*, (*C*) 424

——, Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia, Madej, T. H., *et al.* 554–557

——, Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia, Wheatley, R. G., *et al.* 558–561

——, Indomethacin in the management of postoperative pain, Nissen, I., *et al.* 304–306

——, Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery, Dahl, J. B., *et al.* 4–8

——, Intrathecal morphine-6-glucuronide and bupivacaine for postoperative pain, Coe, A. J., *et al.*, (*ARS*) 221P

——, Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy, Joris, J., *et al.* 341–345

——, Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers, Dahl, J. B., *et al.* 117–121

——, Pre-emptive analgesia, McQuay, H. J., (*E*) 1–3

——, Pre-emptive extradural analgesia, Dahl, J. B., *et al.*, (*C*) 664–665

——, Pre-emptive extradural analgesia, Wilder-Smith, O. H. G., *et al.*, (*C*) 663–664

Pain, threshold, Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers, Dahl, J. B., *et al.* 117–121

Parasympathetic nervous system, atropine, Current management of postoperative nausea and vomiting, Rowbotham, D. J. 46–59S

Parasympathetic nervous system, hyoscine, Current management of postoperative nausea and vomiting, Rowbotham, D. J. 46–59S

Partial pressure, arterial, Components of the inspired to arterial isoflurane partial pressure difference, Matson, A. M., *et al.*, (*ARS*) 528–529P

Partial pressure, end-tidal, Components of the inspired to arterial isoflurane partial pressure difference, Matson, A. M., *et al.*, (*ARS*) 528–529P

Partial pressure, isoflurane, Components of the inspired to arterial isoflurane partial pressure difference, Matson, A. M., *et al.*, (*ARS*) 528–529P

Partial pressure, oxygen, Derivation of $\dot{V}/\dot{Q}$ from the position of the $P\text{I}_{O_2}$ *vs* $S\text{p}_{O_2}$ curve, Sapsford, D. J., *et al.*, (*ARS*) 541P

Pharmacodynamics, Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly, McCarthy, G. J., *et al.* 281–283

——, Etomidate shortens the onset time of neuromuscular block, Gill, R. S., *et al.* 444–446

——, Fade during recovery from vecuronium, Campkin, N. T. A., *et al.*, (*C*) 226–227

——, Influence of body weight and gender on the pharmacodynamics of atracurium, Devlin, J. C., *et al.*, (*ARS*) 217–218P

——, Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia, Mayer, M., *et al.* 511–512

——, Onset of neuromuscular block in myasthenic patients, Baraka, A., (*C*) 227–228

——, Pharmacodynamic stability of a mixture of propofol and alfentanil, Taylor, I. N., *et al.* 168–171

——, Pharmacodynamics of mivacurium chloride in the cirrhotic patient, Devlin, J. C., *et al.*, (*ARS*) 534–535P

——, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585

——, Relationship of the train-of-four ratio to plasma atracurium concentration, Parker, C. J. R., *et al.* 274–280

Pharmacokinetics, alfentanil, Disposition of alfentanil in burns patients, McFie, A. G., *et al.* 447–450

Pharmacokinetics, atracurium, Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium, Parker, C. J. R., *et al.* 439–443

——, Relationship of the train-of-four ratio to plasma atracurium concentration, Parker, C. J. R., *et al.* 274–280

Pharmacokinetics, bupivacaine, Elimination of bupivacaine and pethidine from the rabbit feto–placental unit, Carson, R. J., *et al.* 150–153

Pharmacokinetics, etomidate, Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum, Esener, Z., *et al.* 586–588

Pharmacokinetics, lignocaine, Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery, Michael, S., *et al.* 577–579

Pharmacokinetics, liver, Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery, Lange, H., *et al.* 478–481

Pharmacokinetics, methohexitone, Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery, Lange, H., *et al.* 478–481

Pharmacokinetics, mivacurium, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585

Pharmacokinetics, models, One-compartment kinetics, Norman, J. 387–396

Pharmacokinetics, pethidine, Elimination of bupivacaine and pethidine from the rabbit feto–placental unit, Carson, R. J., *et al.* 150–153

Pharmacokinetics, rocuronium, Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia, Mayer, M., *et al.* 511–512

Pharmacokinetics, thiopentone, Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum, Esener, Z., *et al.* 586–588

Pharmacokinetics, uptake, Effect of halothane on [^{3}H]methylcholine uptake into rat brain synaptosomes, Griffiths, R., *et al.*, (*ARS*) 530P
——, Influence of body weight and gender on the pharmacodynamics of atracurium, Devlin, J. C., *et al.*, (*ARS*) 217–218P
Pharmacokinetics, vecuronium, Etomidate shortens the onset time of neuromuscular block, Gill, R. S., *et al.* 444–446
——, Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia, Mayer, M., *et al.* 511–512
Pharmacology, 5-HT antagonists, 5-HT$_3$ antagonists and postoperative nausea and vomiting, Russell, D., *et al.* 63–68S
Pharmacology, agonists opioid, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, Micol, J. A., *et al.* 487–491
Pharmacology, blood loss, Perioperative blood loss and its reduction: the role of the anaesthetist, Simpson, P. 498–507
Pharmacology, dobutamine, Effect of dobutamine on oxygen supply and uptake in healthy volunteers, Bhatt, S. B., *et al.* 298–303
Pharmacology, dose–response, Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly, McCarthy, G. J., *et al.* 281–283
——, Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia, Browne, B. L., *et al.* 570–576
Pharmacology, ketanserin, Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam–fentanyl or isoflurane anaesthesia, Olsen, K. S., *et al.* 263–268
Pharmacology, synergism, Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil, Short, T. G., *et al.* 162–167
——, Synergistic interaction between midazolam and propofol, McClune, S., *et al.* 240–245
Physics, baricity, Comparison of hypertonic saline (5%), isotonic saline and Ringer's lactate solutions for fluid preloading before lumbar extradural anaesthesia, Veroli, P., *et al.* 461–464
——, Spread of spinal anaesthesia, Adkisson, G. H., (*C*) 328
——, Spread of spinal anaesthesia, Tuominen, M., *et al.*, (*C*) 328–329
Physiotherapy, Effect of physiotherapy on EEG spectral derivatives in sedated patients in the intensive care unit, Wang, D. Y., *et al.*, (*ARS*) 221–222P
Pig, Action of ketamine on isolated porcine trachealis muscle, Hatch, D. J., *et al.*, (*ARS*) 217P
——, Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood–brain barrier, Werba, A., *et al.* 382–386
Placenta, Influence of vitamin B$_{12}$ status on the inactivation of methionine synthase by nitrous oxide, Landon, M. J., *et al.* 81–86
Placenta, drug distribution, Elimination of bupivacaine and pethidine from the rabbit feto–placental unit, Carson, R. J., *et al.* 150–153
Plasma Volume Expansion, Baron, J.-F., (editor), (*R*) 668
Position, effects, Influence of temperature and posture changes on evoked electromyography, Smith, D. C., *et al.*, (*ARS*) 223P
Position, sitting, Training in fibreoptic intubation, Peskett, M. J., (*C*) 331
Position, supine, Gastric regurgitation during general anaesthesia in the supine position with the laryngeal and face mask airways, El Mikatti, N., *et al.*, (*ARS*) 529–530P
Potency, anaesthetic, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects on circulatory function, Huang, Y. F., *et al.* 368–374
——, Somatic movement and oesophageal motility during isoflurane anaesthesia, Mather, C., *et al.* 40–44
——, Sternocleidomastoid muscle contractility at different levels of isoflurane anaesthesia in humans, Oshima, T., *et al.* 236–239
Potency, anaesthetic, age factors, Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients, Peacock, J. E., *et al.* 363–367
Potency, anaesthetic, ED$_{50}$, Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia, Browne, B. L., *et al.* 570–576
Potency, anaesthetic, MAC, Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia, Katoh, T., *et al.* 259–262
——, Components of the inspired to arterial isoflurane partial pressure difference, Matson, A. M., *et al.*, (*ARS*) 528–529P
Potency, drug, tolerance, Probable resistance to vecuronium involving the 17-hydroxy metabolite, Cozanitis, D. A., (*C*) 110–111
——, Repeated resistance to non-depolarizing neuromuscular blocking drugs in a patient with multiple myeloma, Ip Yam, C., *et al.*, (*C*) 111
Pregnancy, A longitudinal study of gastric emptying of a test meal during pregnancy, Magides, A. D., *et al.*, (*ARS*) 529P
——, Life-threatening acute respiratory distress in late pregnancy, Mettam, I. M., *et al.* 420–421
Pregnancy, aspirin therapy, Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), Macdonald, R., (*C*) 109–110
——, Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), de Swiet, M., *et al.*, (*C*) 109
——, Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects, Orlikowski, C. E. P., *et al.* 159–161
Premedication, Anaesthetic factors contributing to postoperative nausea and vomiting, Rabey, P. G., *et al.* 40–45S
——, Current management of postoperative nausea and vomiting, Rowbotham, D. J. 46–59S
——, Effect of preoperative opioid administration on postoperative pain, Dahl, J. B., *et al.*, (*C*) 424–425
——, Effect of preoperative opioid administration on postoperative pain, Katz, J., *et al.*, (*C*) 424
——, Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery, Escolano, F., *et al.* 404–406
Principles of Measurement and Monitoring in Anaesthesia and Intensive Care, 3rd Edn, Sykes, M. K., *et al.*, (*R*) 666
Protein, binding, Disposition of alfentanil in burns patients, McFie, A. G., *et al.* 447–450
——, *In vitro* displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs, Williams, W. R., *et al.* 508–510
——, Repeated resistance to non-depolarizing neuromuscular blocking drugs in a patient with multiple myeloma, Ip Yam, C., *et al.*, (*C*) 111
Protein, human serum albumin, Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin, O'Donnell, N. G., *et al.* 70–74
Psychological responses, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64
Psychological responses, postoperative, Incidence and severity of postoperative nausea and vomiting in patients exposed to positive intraoperative suggestions, Williams, A. R., *et al.*, (*ARS*) 216–217P
——, Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion, Bethune, D. W., *et al.* 197–199
Psychological responses, unconscious perception, Anaesthetic factors contributing to postoperative nausea and vomiting, Rabey, P. G., *et al.* 40–45S
——, Incidence and severity of postoperative nausea and vomiting in patients exposed to positive intraoperative suggestions, Williams, A. R., *et al.*, (*ARS*) 216–217P
Publications, Dual publication of abstracts, Campbell, I. T., (*C*) 227
——, Dual publication of abstracts, Smith, G., (*C*) 227

Rabbit, Elimination of bupivacaine and pethidine from the rabbit feto–placental unit, Carson, R. J., *et al.* 150–153
——, Propofol anticonvulsant activity in experimental epileptic status, De Riu, P. L., *et al.* 177–181
Rat, Effect of halothane on [^{3}H]methylcholine uptake into rat brain synaptosomes, Griffiths, R., *et al.*, (*ARS*) 530P
——, Effects of halothane on cultured neurones, Winlow, W., *et al.*, (*ARS*) 530–531P
——, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64
——, Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver, Reckendorfer, H., *et al.* 288–291
——, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, Micol, J. A., *et al.* 487–491

——, Isoflurane inhibits insulin secretion from isolated rat pancreatic islets of Langerhans, Desborough, J. P., *et al.*, (*ARS*) 532P
——, Peripheral nerve injury caused by injection needles used in regional anaesthesia: influence of bevel configuration, studied in a rat model, Rice, A. S. C., *et al.* 433–438
——, Relative pre- and postjunctional effects of a new vecuronium analogue, Org 9426, at the rat neuromuscular junction, Tian, L., *et al.* 284–287
Receptors, opioid, Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat, Micol, J. A., *et al.* 487–491
Records, anaesthesia, A National Database on hepatitis after exposure to inhaled anaesthetics, Kenna, J. G., *et al.*, (*C*) 228–229
Recovery, Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia, Katoh, T., *et al.* 259–262
Recovery, cognitive, Recovery of cognitive functions after anaesthesia with desflurane or isoflurane and nitrous oxide, Tsai, S. K., *et al.* 255–258
Recovery, neurological, Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome, Stephan, H., *et al.* 51–57
Recovery, psychomotor, EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism, Engelhardt, W., *et al.* 75–80
Reflexes, spinal, Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers, Dahl, J. B., *et al.* 117–121
Reflexes, threshold, Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers, Dahl, J. B., *et al.* 117–121
Research, emesis, The study of postoperative nausea and vomiting, Korttila, K. 20–23S
Researches Practical and Physiological on Etherization, Pirogoff, N., *et al.*, (*R*) 333
Respiratory Monitoring (*Contemporary Management in Critical Care* series), Tobin, M. J., (editor), (*R*) 666
Risk, A logistic regression model for risk stratification of fixed patient factors for postoperative emesis, Palazzo, M. G. A., *et al.*, (*ARS*) 530P
——, Risk factors for oxygen desaturation during sleep, after abdominal surgery, Beydon, L., *et al.* 137–142

Safety, drug, Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs, Laroche, D., *et al.* 611–614
——, Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs, Finegan, B. A., *et al.* 492–497
——, *In vitro* displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs, Williams, W. R., *et al.* 508–510
Safety, equipment, Bacterial retention properties of heat and moisture exchange filters, Lee, M. G., *et al.* 522–525
——, Damage to coaxial breathing systems, Liddle, M. W. D., (*C*) 425
——, Damage to coaxial breathing systems, Williams, A. R., (*C*) 425
——, Metallic fragments and the combined spinal–extradural technique, Carrie, L. E. S., (*C*) 662–663
——, Metallic fragments and the combined spinal–extradural technique, Eldor, J., (*C*) 663
——, Overdose of opioid from patient-controlled analgesia pumps, Notcutt, W. G., *et al.* 95–97
——, Where is the bobbin? Bras, P., *et al.*, (*ARS*) 539P
Safety, techniques, Extradural abscess complicating extradural anaesthesia for Caesarean section, Ngan Kee, W. D., *et al.* 647–652
Screening, Evaluation of spin resonance spectroscopy of red blood cell membranes to detect malignant hyperthermia susceptibility, Halsall, P. J., *et al.* 471–473
——, Is muscle biopsy for malignant hyperthermia diagnosis still necessary? Ball, S. P., *et al.*, (*ARS*) 222–223P
——, Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? Ellis, F. R., *et al.* 468–470
——, Radioimmunoassay tests and anaphylaxis, Imray, I. McG., *et al.*, (*C*) 543–544
——, Unnecessary preoperative investigations in children, Wilson, A., *et al.*, (*C*) 425
Sedation, EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism, Engelhardt, W., *et al.* 75–80
——, EEG and memory effects of low-dose infusions of propofol, Veselis, R. A., *et al.* 246–254
——, Effect of physiotherapy on EEG spectral derivatives in sedated patients in the intensive care unit, Wang, D. Y., *et al.*, (*ARS*) 221–222P
Serotonin (5-hydroxytryptamine), The role of 5-HT in postoperative nausea and vomiting, Bunce, K. T., *et al.* 60–62S
Serotonin (5-hydroxytryptamine), antagonism, 5-HT$_3$ antagonists and postoperative nausea and vomiting, Russell, D., *et al.* 63–68S
Sheep, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects on circulatory function, Huang, Y. F., *et al.* 368–374
Sleep, Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats, Murayama, T., *et al.* 61–64
——, Risk factors for oxygen desaturation during sleep, after abdominal surgery, Beydon, L., *et al.* 137–142
Solubility, partition coefficients, Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia, Katoh, T., *et al.* 259–262
Spinal cord, evoked potentials, Some effects of isoflurane on I waves of the motor evoked potential, Hicks, R. G., *et al.* 130–136
Standard Operating Procedures for Investigators, Ball, G., *et al.*, (*R*) 231
Standards of Care in Anaesthesia, Taylor, T. H., *et al.*, (*R*) 334
Statistics, The study of postoperative nausea and vomiting, Korttila, K. 20–23S
Stress, hormonal response, EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects, Laycock, G. J. A., *et al.* 356–362
Stress, metabolic response, EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects, Laycock, G. J. A., *et al.* 356–362
Surgery, abdominal, Extradural fentanyl–bupivacaine compared with patient controlled analgesia using i.v. morphine after upper abdominal surgery, Wright, P. M. C., *et al.*, (*ARS*) 219–220P
——, Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia, Madej, T. H., *et al.* 554–557
——, Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia, Wheatley, R. G., *et al.* 558–561
——, Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery, Dahl, J. B., *et al.* 4–8
——, Pre-emptive extradural analgesia, Dahl, J. B., *et al.*, (*C*) 664–665
——, Pre-emptive extradural analgesia, Wilder-Smith, O. H. G., *et al.*, (*C*) 663–664
——, Risk factors for oxygen desaturation during sleep, after abdominal surgery, Beydon, L., *et al.* 137–142
——, Somatic movement and oesophageal motility during isoflurane anaesthesia, Mather, C., *et al.* 40–44
Surgery, cardiovascular, Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome, Stephan, H., *et al.* 51–57
——, Comparison of propofol–fentanyl and isoflurane–fentanyl for maintenance of anaesthesia during cardiac surgery, Phillips, A. S., *et al.*, (*ARS*) 211–212P
——, EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects, Laycock, G. J. A., *et al.* 356–362
——, Influence of myocardial preservation technique on perioperative neutrophil activity in patients undergoing coronary artery graft surgery, Columb, M. O., *et al.*, (*ARS*) 211P
——, The role of enoximone in cardiac surgery, Boldt, J., *et al.* 45–50
Surgery, cholecystectomy, Changes in respiratory function after laparoscopic cholecystectomy, Martin, C. S., *et al.*, (*ARS*) 526P
——, Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy, Joris, J., *et al.* 341–345
Surgery, cleft palate, Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery, Michael, S., *et al.* 577–579
Surgery, day-case, Postoperative nausea and vomiting in day-case surgery, Wetchler, B. V. 33–39S
Surgery, endarterectomy, Comparison of the effects of methoxamine and phenylephrine on middle cerebral artery velocity during carotid endarterectomy, Kaneko, K., *et al.*, (*ARS*) 537P

Surgery, gastrointestinal, Effect of diclofenac on renal function and prostacyclin generation after surgery, Power, I., *et al.* 451–456

Surgery, gynaecological, Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section, Wennberg, E., *et al.* 13–18

——, Comparison of extradural administration of sufentanil, morphine and sufentanil–morphine combination after Caesarean section, Dottrens, M., *et al.* 9–12

——, Effect of four different maintenance anaesthetic techniques for minor surgery on gastric emptying, Bennett, M. W. R., *et al.*, (*ARS*) 220P

——, Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers, Dahl, J. B., *et al.* 117–121

——, The importance of activity and pretreatment in the prevention of suxamethonium myalgias, Oxorn, D. C., *et al.* 200–201

Surgery, laparoscopy, Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy, Joris, J., *et al.* 341–345

——, Ventilatory effects of laparoscopy under general anaesthesia, Puri, G. D., *et al.*, (*C*) 543

——, Ventilatory effects of laparoscopy under general anaesthesia, Shankar, K. B., *et al.*, (*C*) 542–543

Surgery, laparotomy, Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy, Joris, J., *et al.* 341–345

Surgery, metabolic response, Interleukin-6 and the metabolic response to surgery, Hall, G. M., *et al.*, (*E*) 337–338

——, Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy, Joris, J., *et al.* 341–345

Surgery, miscellaneous, Pharmacodynamic stability of a mixture of propofol and alfentanil, Taylor, I. N., *et al.* 168–171

Surgery, ophthalmological, Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma, Chaudhri, S., *et al.* 607–610

——, Postoperative oxygenation in the elderly after ophthalmic surgery: comparison of local and general anaesthesia, McCarthy, G., *et al.*, (*ARS*) 213–214P

——, The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses, Lamb, K., *et al.* 143–147

Surgery, oral, Four anaesthetic techniques for day-case oral surgery, Martlew, R., *et al.*, (*ARS*) 219P

Surgery, orthopaedic, Blood loss during total hip replacement, McSwiney, M., *et al.*, (*C*) 331–332

——, Blood loss during total hip replacement, Wittmann, P. H., *et al.*, (*C*) 332

——, Ketorolac trometamol for postoperative analgesia after orthopaedic surgery, Kinsella, J., *et al.* 19–22

Surgery, plastic, Disposition of alfentanil in burns patients, McFie, A. G., *et al.* 447–450

——, Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol, Murray, J. M., *et al.* 643–644

Surgery, reconstructive, Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol, Murray, J. M., *et al.* 643–644

Surgery, spinal, Indomethacin in the management of postoperative pain, Nissen, I., *et al.* 304–306

——, Some effects of isoflurane on I waves of the motor evoked potential, Hicks, R. G., *et al.* 130–136

Surgery, thoracic, Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis, Jedeikin, R., *et al.* 349–351

——, Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy, Welte, M., *et al.* 637–639

——, Patient-controlled analgesia after thoracotomy: thoracic extradural *vs* i.v. fentanyl, Keenan, G. M. A., *et al.*, (*ARS*) 533P

——, Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy, Merry, A. F., *et al.* 92–94

Surgery, transplantation, Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure, Cook, D. R., *et al.* 580–585

Surgery, urological, Postdural puncture headache in urological surgery: an evaluation of the atraumatic spinal needle, Harrison, D. A., *et al.*, (*ARS*) 540–541P

——, Topical anaesthesia for extracorporeal shock wave lithotripsy, McDonald, P. F., *et al.* 399–400

Surgery, vascular, Fatal tracheal compression after haemorrhage into the axilla, Cook, L. B., *et al.* 322–324

——, Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery, Stühmeier, K. D., *et al.* 602–606

——, Risk factors for oxygen desaturation during sleep, after abdominal surgery, Beydon, L., *et al.* 137–142

——, Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: comparison with the thermodilution technique, Ryan, T., *et al.* 101–104

Sympathetic nervous system, clonidine, Alcohol withdrawal treatment with clonidine, Robinson, B. J., *et al.*, (*C*) 328

Sympathetic nervous system, dobutamine, Effect of dobutamine on oxygen supply and uptake in healthy volunteers, Bhatt, S. B., *et al.* 298–303

Sympathetic nervous system, ephedrine, Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section, Wennberg, E., *et al.* 13–18

Sympathetic nervous system, ganglia, Fentanyl inhibits evoked [^{3}H]noradrenaline release from human neuroblastoma cells, Atcheson, R., *et al.*, (*ARS*) 531P

Sympathetic nervous system, methoxamine, Comparison of the effects of methoxamine and phenylephrine on middle cerebral artery velocity during carotid endarterectomy, Kaneko, K., *et al.*, (*ARS*) 537P

Sympathetic nervous system, phenylephrine, Comparison of the effects of methoxamine and phenylephrine on middle cerebral artery velocity during carotid endarterectomy, Kaneko, K., *et al.*, (*ARS*) 537P

Sympathetic nervous system, sympathoadrenal responses, Fentanyl inhibits evoked [^{3}H]noradrenaline release from human neuroblastoma cells, Atcheson, R., *et al.*, (*ARS*) 531P

——, The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses, Lamb, K., *et al.* 143–147

Temperature, body, Influence of temperature and posture changes on evoked electromyography, Smith, D. C., *et al.*, (*ARS*) 223P

Temperature, monitoring, Skin injury with a pulse oximeter, Bethune, D. W., *et al.*, (*C*) 665

——, Skin injury with a pulse oximeter, Pettersen, B., *et al.*, (*C*) 665

Temperature, skin, Effects of skin blood flow and temperature on skin–electrode impedance and offset potential, Smith, D. C., (*ARS*) 223P

——, Skin injury with a pulse oximeter, Bethune, D. W., *et al.*, (*C*) 665

——, Skin injury with a pulse oximeter, Pettersen, B., *et al.*, (*C*) 665

The Ageing Surgical Patient—Anaesthetic, Operative and Medical Management, Crosby, D. L., *et al.*, (editors), (*R*) 426–427

The Critical Care Drug Handbook, Zaloga, G. P., (*R*) 548

The Management of Acute Pain, Park, G., *et al.*, (*R*) 548

The Obstructed Airway (Ministry of Defence training film), (*R*) 427

The Oxygen Status of Arterial Blood, Zander, R., *et al.*, (editors), (*R*) 333

The Pediatric Anesthesia Handbook, Bell, C., *et al.*, (editors), (*R*) 230

Theories of anaesthetic action, cellular mechanisms, Action of ketamine on isolated porcine trachealis muscle, Hatch, D. J., *et al.*, (*ARS*) 217P

——, Fentanyl inhibits evoked [^{3}H]noradrenaline release from human neuroblastoma cells, Atcheson, R., *et al.*, (*ARS*) 531P

Theories of anaesthetic action, molecular, Molecular actions of racemic ketamine on human CNS sodium channels, Frenkel, C., *et al.* 292–297

Thoracic Anesthesia, 2nd Edn, Kaplan, J. A., (editor), (*R*) 112

Toxicity, Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs, Finegan, B. A., *et al.* 492–497

Toxicity, hepatic, Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver, Reckendorfer, H., *et al.* 288–291

Toxicity, local anaesthetics, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects on circulatory function, Huang, Y. F., *et al.* 368–374

——, Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure, Putensen, C., *et al.* 513–516

Toxicity, metabolites, Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver, Reckendorfer, H., *et al.* 288–291

Transfusion, Blood loss during total hip replacement, McSwiney, M., *et al.*, (*C*) 331–332

——, Blood loss during total hip replacement, Wittmann, P. H., *et al.*, (*C*) 332

——, Massive blood transfusion, Donaldson, M. D. J., *et al.* 621–630

Transfusion, complications, Massive blood transfusion, Donaldson, M. D. J., *et al.* 621–630

Transfusion, stored blood, Plasma antioxidant activity in stored blood, Myers, D. S., *et al.*, (*ARS*) 222P

Veins, cannulation, Pressor response to venous cannulation and effect of local anaesthetic infiltration, Langham, B. T., *et al.*, (*ARS*) 537–538P

Veins, complications, Venous sequelae of diclofenac, Berry, C. B., *et al.*, (*C*) 332

——, Venous sequelae of diclofenac, Gopinath, R., (*C*) 332

Veins, jugular, cannulation, The Siterite ultrasound machine: an aid to internal jugular vein cannulation? Armstrong, P. J., *et al.*, (*ARS*) 533–534P

Ventilation, Advances in cardiopulmonary resuscitation, Baskett, P. J. F. 182–193

Ventilation, airway pressure, Auto-PEEP, lung volume and sternotomy, Fletcher, R., (*ARS*) 527P

Ventilation, airway resistance, Effect of fentanyl on ventilatory resistances during barbiturate general anaesthesia, Cohendy, R., *et al.* 595–598

Ventilation, analgesics, effects of, Effect of fentanyl on ventilatory resistances during barbiturate general anaesthesia, Cohendy, R., *et al.* 595–598

Ventilation, apnoea, Use of nasal oxygen cannulae to monitor postoperative breathing, Nimmo, A. F., *et al.*, (*ARS*) 539–540P

Ventilation, carbon dioxide response, Parallel Lack breathing system: fresh gas flow requirements during spontaneous ventilation, Ooi, R., *et al.*, (*ARS*) 216P

——, Rebreathing in the Magill breathing system, Soni, N., *et al.*, (*ARS*) 215–216P

——, Ventilatory effects of laparoscopy under general anaesthesia, Puri, G. D., *et al.*, (*C*) 543

——, Ventilatory effects of laparoscopy under general anaesthesia, Shankar, K. B., *et al.*, (*C*) 542–543

Ventilation, failure, Life-threatening acute respiratory distress in late pregnancy, Mettam, I. M., *et al.* 420–421

Ventilation, fresh gas flow, Parallel Lack breathing system: fresh gas flow requirements during spontaneous ventilation, Ooi, R., *et al.*, (*ARS*) 216P

——, Rebreathing in the Magill breathing system, Soni, N., *et al.*, (*ARS*) 215–216P

Ventilation, mechanical, A new look at the breath of life, Ward, M. E., (*E*) 339–340

——, A new technique for two-hand bag valve mask ventilation, Thomas, A. N., *et al.* 397–398

——, Bacterial overgrowth and gastric dysfunction, Inglis, T., (*C*) 545

——, Bacterial overgrowth and gastric dysfunction, Wilder-Smith, C. H., (*C*) 545

——, Comparison of the use of the laryngeal mask and face mask by inexperienced personnel, Tolley, P. M., *et al.* 320–321

——, Mouth mask ventilation: use of a Pall Ultipor breathing system and effect of mask design, Thomas, A. N., *et al.*, (*ARS*) 527–528P

Ventilation, spontaneous, Determination of the onset of rebreathing: comparison of six methods during spontaneous ventilation, Barrie, J. R., *et al.*, (*ARS*) 527P

——, Parallel Lack breathing system: fresh gas flow requirements during spontaneous ventilation, Ooi, R., *et al.*, (*ARS*) 216P

Ventilation, ventilation–perfusion, Derivation of $\dot{V}/\dot{Q}$ from the position of the P_{IO_2} *vs* Sp_{O_2} curve, Sapsford, D. J., *et al.*, (*ARS*) 541P

Vitamins, B$_{12}$, Influence of vitamin B$_{12}$ status on the inactivation of methionine synthase by nitrous oxide, Landon, M. J., *et al.* 81–86

Vomiting, antiemetics, Anaesthetic factors contributing to postoperative nausea and vomiting, Rabey, P. G., *et al.* 40–45S

——, Current management of postoperative nausea and vomiting, Rowbotham, D. J. 46–59S

——, Postoperative nausea and vomiting in day-case surgery, Wetchler, B. V. 33–39S

Vomiting, incidence, A logistic regression model for risk stratification of fixed patient factors for postoperative emesis, Palazzo, M. G. A., *et al.*, (*ARS*) 530P

——, Incidence and severity of postoperative nausea and vomiting in patients exposed to positive intraoperative suggestions, Williams, A. R., *et al.*, (*ARS*) 216–217P

——, The study of postoperative nausea and vomiting, Korttila, K. 20–23S

Vomiting, nausea, 5-HT$_3$ antagonists and postoperative nausea and vomiting, Russell, D., *et al.* 63–68S

——, Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section, Wennberg, E., *et al.* 13–18

——, Incidence and severity of postoperative nausea and vomiting in patients exposed to positive intraoperative suggestions, Williams, A. R., *et al.*, (*ARS*) 216–217P

——, Introduction, Rowbotham, D. J., *et al.* 1S

——, Postoperative nausea and vomiting in day-case surgery, Wetchler, B. V. 33–39S

——, The role of 5-HT in postoperative nausea and vomiting, Bunce, K. T., *et al.* 60–62S

——, The study of postoperative nausea and vomiting, Korttila, K. 20–23S

Vomiting, nausea, anaesthetic factors, Anaesthetic factors contributing to postoperative nausea and vomiting, Rabey, P. G., *et al.* 40–45S

Vomiting, nausea, pathogenesis, Physiology of nausea and vomiting: speculations on the mechanisms of postoperative nausea and vomiting, Andrews, P. L. R. 2–19S

——, Surgical and patient factors involved in postoperative nausea and vomiting, Lerman, J. 24–32S

Vomiting, nausea, patient factors, A logistic regression model for risk stratification of fixed patient factors for postoperative emesis, Palazzo, M. G. A., *et al.*, (*ARS*) 530P

——, Surgical and patient factors involved in postoperative nausea and vomiting, Lerman, J. 24–32S

Vomiting, nausea, physiology, Physiology of nausea and vomiting: speculations on the mechanisms of postoperative nausea and vomiting, Andrews, P. L. R. 2–19S

Vomiting, nausea, surgical factors, Gastric regurgitation during general anaesthesia in the supine position with the laryngeal and face mask airways, El Mikatti, N., *et al.*, (*ARS*) 529–530P

——, Surgical and patient factors involved in postoperative nausea and vomiting, Lerman, J. 24–32S

Year Book of Anesthesia, 1991, Miller, R. D., *et al.*, (editors), (*R*) 113

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CONTENTS

JULY

EDITORIAL: Pre-emptive analgesia 1
H. J. McQuay

ORIGINAL ARTICLES

Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery 4
J. B. Dahl, B. L. Hansen, N. C. Hjortsø, C. J. Erichsen, S. Møiniche and H. Kehlet

Comparison of extradural administration of sufentanil, morphine and sufentanil–morphine combination after Caesarean section 9
M. Dottrens, K. Rifat and D. R. Morel

Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section 13
E. Wennberg, I. Frid, H. Haljamäe and H. Norén

Ketorolac trometamol for postoperative analgesia after orthopaedic surgery 19
J. Kinsella, A. C. Moffat, J. A. Patrick, J. W. Prentice, C. S. McArdle and G. N. C. Kenny

Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol 23
P. Barker, J. A. Langton, I. G. Wilson and G. Smith

Comparison of atracurium-induced neuromuscular block in rectus abdominis and hand muscles of man. 26
J. M. Saddler, L. F. Marks and J. Norman

Factors affecting magnitude and time course of neuromuscular block produced by suxamethonium 29
L. E. H. Vanlinthout, J. van Egmond, T. de Boo, J. G. C. Lerou, R. A. Wevers and L. H. D. J. Booij

Haemodynamic effects of isoflurane during propofol anaesthesia 36
C. Verborgh, D. Verbessem and F. Camu

Somatic movement and oesophageal motility during isoflurane anaesthesia 40
C. Mather, S. Raftery and C. Prys-Roberts

The role of enoximone in cardiac surgery 45
J. Boldt, C. Knothe, B. Zickmann, M. Ballesteros, W. Russ, F. Dapper and G. Hempelmann

Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome. 51
H. Stephan, A. Weyland, S. Kazmaier, T. Henz, S. Menck and H. Sonntag

Does etomidate cause haemolysis? 58
A. E. Nebauer, A. Doenicke, R. Hoernecke, R. Angster and M. Mayer

Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats 61
T. Murayama, K. Shingu, T. Ogawa, K. Tomoda, K. Shindo, S. Tamai and K. Mori

Comparison of the relaxant effects of diazepam, flunitrazepam and midazolam on airway smooth muscle .. 65
Y. Koga, S. Sato, N. Sodeyama, M. Takahashi, M. Kato, N. Iwatsuki and Y. Hashimoto

Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin 70
N. G. O'Donnell, C. P. McSharry, P. C. Wilkinson and A. J. Asbury

EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism 75
W. Engelhardt, K. Friess, E. Hartung, M. Sold and T. Dierks

Influence of vitamin B_{12} status on the inactivation of methionine synthase by nitrous oxide 81
M. J. Landon, P. Creagh-Barry, S. McArthur and A. Charlett

In vitro diagnosis of malignant hyperthermia: influence of electrical stimulation on the contracture response to caffeine 87
L. Heytens, J. J. Martin and L. L. Bossaert

SHORT COMMUNICATION

Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy 92
A. F. Merry, G. J. Wardall, R. J. Cameron, M. J. Peskett and C. J. Wild

CASE REPORT

Overdose of opioid from patient-controlled analgesia pumps 95
W. G. Notcutt, P. Knowles and R. Kaldas

APPARATUS

Tracheal models which simulate the compliance of the adult male trachea 98
N. Lomholt

Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: comparison with the thermodilution technique 101
T. Ryan, R. Page, D. Bouchier-Hayes and A. J. Cunningham

Continuous collection of pulse oximetry data: a new, inexpensive portable computerized method 105
A. L. Ronald, G. P. Ramayya and W. A. Chambers

CORRESPONDENCE

Intrathecal diamorphine–bupivacaine during labour ... 108
The United Kingdom as seen by a Japanese anaesthetist 108
Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) 109
Atracurium and histamine 110
Probable resistance to vecuronium involving the 17-hydroxy metabolite 110
Repeated resistance to non-depolarizing neuromuscular blocking drugs in a patient with multiple myeloma .. 111

BOOK REVIEWS

Thoracic Anesthesia, 2nd Edn 112
Drug Infusions in Anesthesiology 112
Infection and the Anaesthetist 112
Lecture Notes on Anaesthetics, 4th Edn 113
Year Book of Anesthesia, 1991 113

AUGUST

EDITORIAL: Prolonged postoperative oxygen therapy. 115
C. D. Hanning

ORIGINAL ARTICLES

Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers 117
J. B. Dahl, C. J. Erichsen, A. Fuglsang-Frederiksen and H. Kehlet

Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane. 122
D. E. F. Newton, C. Thornton, K. M. Konieczko, C. Jordan, N. R. Webster, N. P. Luff, C. D. Frith and C. J. Doré

Some effects of isoflurane on I waves of the motor evoked potential 130
R. G. Hicks, I. J. Woodforth, M. R. Crawford, J. P. H. Stephen and D. J. Burke

Risk factors for oxygen desaturation during sleep, after abdominal surgery 137
L. Beydon, J. Hassapopoulos, M.-A. Quera, A. Rauss, J.-P. Becquemin, F. Bonnet, A. Harf and F. Goldenberg

The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses .. 143
K. Lamb, M. F. M. James and P. K. Janicki

Effect of speed of injection of 0.5% plain bupivacaine on the spread of spinal anaesthesia 148
M. Tuominen, M. Pitkänen and P. H. Rosenberg

Elimination of bupivacaine and pethidine from the rabbit feto–placental unit 150
R. J. Carson and F. Reynolds

Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia 154
J. M. Eddleston, M. Maresh, E. L. Horsman, H. Young, P. Lacey and J. Anderton

Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects 159
C. E. P. Orlikowski, A. J. Payne, J. Moodley and D. A. Rocke

Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil 162
T. G. Short, J. L. Plummer and P. T. Chui

Pharmacodynamic stability of a mixture of propofol and alfentanil 168
I. N. Taylor, G. N. C. Kenny and J. B. Glen

Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate 172
M. L. Price, B. Millar, M. Grounds and J. Cashman

Propofol anticonvulsant activity in experimental epileptic status 177
P. L. De Riu, V. Petruzzi, C. Testa, M. Mulas, F. Melis, M. A. Caria and O. Mameli

REVIEW ARTICLE

Advances in cardiopulmonary resuscitation 182
P. J. F. Baskett

SHORT COMMUNICATIONS

Video surveillance of oxygen administration by mask in postoperative patients 194
K. M. Nolan, M. K. Baxter, J. A. Winyard, C. J. Roulson and D. R. Goldhill

Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion 197
D. W. Bethune, S. Ghosh, B. Gray, L. Kerr, I. A. Walker, L. A. Doolan, R. J. Harwood and L. D. Sharples

The importance of activity and pretreatment in the prevention of suxamethonium myalgias 200
D. C. Oxorn, G. S. Whatley, J. W. D. Knox and J. Hooper

Training in fibreoptic tracheal intubation in the North of England 202
P. R. Wood, M. Dresner and P. G. P. Lawler

CASE REPORTS

Skin injury in an infant with pulse oximetry.......... 204
B. Pettersen, U. Kongsgaard and H. Aune

Anaesthetic management of renin secreting nephroblastoma 206
G. A. Charlton, J. Sedgwick and D. N. Sutton

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Belfast Meeting, April 10–11, 1992 .... 210P

CORRESPONDENCE

Recognition and management of difficult airway problems 224
Verapamil and cardiovascular responses to tracheal intubation 225
Fade during recovery from vecuronium 226
Dual publication of abstracts 227
Bedside respiratory measurements with the Siemens–Elema CO_2 Analyzer 227
Onset of neuromuscular block in myasthenic patients .. 227
Oxygen wastage by oxygen–air mixers 228
A National Database on hepatitis after exposure to inhaled anaesthetics 228
Cardiovascular responses to tracheal extubation 229

BOOK REVIEWS

The Pediatric Anesthesia Handbook 230
Advances in Pain Research and Therapy, Volume 18: The Design of Analgesic Clinical Trials 230
Anesthesiology Review 230
Dripps/Eckenhoff/Vandam Introduction to Anaesthesia, 8th Edn. 231
Atlas of the Difficult Airway 231
Standard Operating Procedures for Investigators 231

SEPTEMBER

EDITORIAL: The role of prostaglandins in the control of renal function 233
K. Harris

ORIGINAL ARTICLES

Sternocleidomastoid muscle contractility at different levels of isoflurane anaesthesia in humans 236
T. Oshima, H. Toyooka and K. Amaha

Synergistic interaction between midazolam and propofol 240
S. McClune, A. C. McKay, P. M. C. Wright, C. C. Patterson and R. S. J. Clarke

EEG and memory effects of low-dose infusions of propofol 246
R. A. Veselis, R. A. Reinsel, M. Wroński, P. Marino, W. P. Tong and R. F. Bedford

Recovery of cognitive functions after anaesthesia with desflurane or isoflurane and nitrous oxide 255
S. K. Tsai, C. Lee, W.-F. Kwan and B.-J. Chen

Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia 259
T. Katoh, Y. Suguro, R. Nakajima, T. Kazama and [illegible] Ikeda

Effect of [illegible]ketanserin on global cerebral blood flow and cerebral [illegible] oxygen metabolism during midazolam–fentanyl [illegible] isoflurane anaesthesia 263
K. S. Olsen[illegible] L. Henriksen, H. Dige-Petersen, B. Chraemmer-J[illegible]ørgensen and J. Rosenørn

Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium 269
R. Cooper, R. K. Mirakhur, R. S. J. Clarke and Z. Boules

Relationship of the train-of-four ratio to plasma atracurium concentration 274
C. J. R. Parker and J. M. Hunter

Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly 281
G. J. McCarthy, R. Cooper, J. C. Stanley and R. K. Mirakhur

Relative pre- and postjunctional effects of a new vecuronium analogue, Org 9426, at the rat neuromuscular junction 284
L. Tian, M. P. Mehta, C. Prior and I. G. Marshall

Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver 288
H. Reckendorfer, H. Burgmann, M. Sperlich, G. L. Tüchy, W. Feigl, P. G. Spieckermann, M. Weindlmayr-Göttel and S. Schwarz

Molecular actions of racemic ketamine on human CNS sodium channels 292
C. Frenkel and B. W. Urban

Effect of dobutamine on oxygen supply and uptake in healthy volunteers 298
S. B. Bhatt, R. C. Hutchinson, B. Tomlinson, T. E. Oh and M. Mak

Indomethacin in the management of postoperative pain 304
I. Nissen, K. A. Jensen and J. K. Öhrström

REVIEW ARTICLE

Thrombelastography 307
S. V. Mallett and D. J. A. Cox

SHORT COMMUNICATIONS

Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway 314
P. Barker, J. A. Langton, P. J. Murphy and D. J. Rowbotham

Pain on injection of propofol: comparison of lignocaine with metoclopramide 316
R. Ganta and J. P. H. Fee

Lung function after vecuronium pretreatment in young, healthy patients 318
R. P. Mahajan and J. Laverty

Comparison of the use of the laryngeal mask and face mask by inexperienced personnel 320
P. M. Tolley, A. D. J. Watts and J. A. Hickman

CASE REPORTS

Fatal tracheal compression after haemorrhage into the axilla 322
L. B. Cook and S. Varley

Anaphylactoid or carcinoid? 325
A. M. Batchelor and I. D. Conacher

CORRESPONDENCE

Alcohol withdrawal treatment with clonidine 328
Spread of spinal anaesthesia 328
Propofol in uraemic patients 329
Bleeding time 329
Training in fibreoptic intubation 331
Blood loss during total hip replacement 331
Antenatal assessment for anaesthesia 332
Venous sequelae of diclofenac 332

BOOK REVIEWS

Researches Practical and Physiological on Etherization 333
The Oxygen Status of Arterial Blood 333
Manual of Post-Anesthesia Care 333
Mechanical Ventilation and Assisted Respiration 334
Standards of Care in Anaesthesia 334

OCTOBER

EDITORIALS:

I. Interleukin-6 and the metabolic response to surgery 337
G. M. Hall and J. P. Desborough

II. A new look at the breath of life 339
M. E. Ward

ORIGINAL ARTICLES

Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy 341
J. Joris, I. Cigarini, M. Legrand, N. Jacquet, D. De Groote, P. Franchimont and M. Lamy

Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia 346
P. G. Rabey, P. J. Murphy, J. A. Langton, P. Barker and D. J. Rowbotham

Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis 349
R. Jedeikin, D. Olsfanger, D. Shachor and K. Mansoor

Perioperative continuous monitoring of ST-segment changes in patients undergoing elective Caesarean section 352
T. N. Trotter, J. A. Langton, P. Barker and D. J. Rowbotham

EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects 356
G. J. A. Laycock, I. M. Mitchell, R. D. Paton, S. F. O'B. Donaghey, R. W. Logan and N. S. Morton

Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients 363
J. E. Peacock, S. P. W. Spiers, G. A. McLauchlin, W. C. Edmondson, M. Berthoud and C. S. Reilly

I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: effects of circulatory function 368
Y. F. Huang, R. N. Upton, A. J. Rutten and W. B. Runciman

Effects of graded infusion rates of propofol on regional and global left ventricular function in the dog 375
R. M. Puttick, J. Diedericks, J. W. Sear, J. B. Glen, P. Foëx and W. A. Ryder

Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood–brain barrier 382
A. Werba, H. Gilly, M. Weindlmayr-Goettel, C. K. Spiss, K. Steinbereithner, T. Czech and S. Agoston

REVIEW ARTICLE

One-compartment kinetics 387
J. Norman

SHORT COMMUNICATIONS

A new technique for two-hand bag valve mask ventilation 397
A. N. Thomas, P. T. Dang, J. Hyatt and T. N. Trinh

Topical anaesthesia for extracorporeal shock wave lithotripsy 399
P. F. McDonald and A. M. Berry

Transient bradycardia associated with extradural blood patch after inadvertent dural puncture in parturients 401
P. J. D. Andrews, W. E. Ackerman, M. Juneja, V. Cases-Cristobal and B. M. Rigor

Effects of omeprazole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery 404
F. Escolano, J. Castaño, R. Lopez, E. Bisbe and A. Alcon

Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway 407
B. J. Philips, S. Fergusson, P. Armstrong, F. M. Anderson and J. A. W. Wildsmith

Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation . 409
J. C. Berridge

A method to facilitate regional anaesthesia by detection of mixed nerve action potentials 411
M. Y. K. Wee, A. Geeurickx and S. Wimalaratna

CASE REPORTS

Lumbovertebral syndrome after extradural blood patch 414
M. D. Seeberger and A. Urwyler

Accidental subdural catheterization: radiological evidence of a possible mechanism for spinal cord damage 417
I. M. McMenemin, G. R. J. Sissons and P. Brownridge

Life-threatening acute respiratory distress in late pregnancy 420
I. M. Mettam, T. R. Reddy and F. E. Evans

CORRESPONDENCE

Midazolam and cardioversion 422
Delayed septicaemia after extradural steroid treatment. 422
Steroid therapy and extradural analgesia 423
Insulated regional block needles 423
Effect of preoperative opioid administration on postoperative pain 424
Damage to coaxial breathing systems 425
Unnecessary preoperative investigations in children.... 425

BOOK REVIEWS

Atlas of Regional Anaesthesia 426
The Ageing Surgical Patient—Anaesthetic, Operative and Medical Management 426
The Obstructed Airway 427
Adult Respiratory Distress Syndrome 427

NOVEMBER

EDITORIALS:

I. Peripheral nerve damage and regional anaesthesia 429
W. A. Chambers

II. The National Confidential Enquiry into Perioperative Deaths 1990 431
S. G. Graham

ORIGINAL ARTICLES

Peripheral nerve injury caused by injection needles used in regional anaesthesia: the influence of bevel configuration, studied in a rat model 433
A. S. C. Rice and S. B. McMahon

Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium 439
C. J. R. Parker, J. M. Hunter and S. L. Snowdon

Etomidate shortens the onset time of neuromuscular block 444
R. S. Gill and R. P. F. Scott

Disposition of alfentanil in burns patients 447
A. G. Macfie, A. D. Magides and C. S. Reilly

Effect of diclofenac on renal function and prostacyclin generation after surgery 451
I. Power, A. D. Cumming and G. C. Pugh

Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic 457
C. H. Blumgart, D. Ryall, B. Dennison and L. M. Thompson-Hill

Comparison of hypertonic saline (5%), isotonic saline and Ringer's lactate solutions for fluid preloading before lumbar extradural anaesthesia 461
P. Veroli and D. Benhamou

Cricoid pressure may prevent insertion of the laryngeal mask airway 465
J. M. Ansermino and C. E. Blogg

Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? 468
F. R. Ellis, P. J. Halsall and P. M. Hopkins

Evaluation of spin resonance spectroscopy of red blood cell membranes to detect malignant hyperthermia susceptibility 471
P. J. Halsall, F. R. Ellis and P. F. Knowles

Fractional delivery of fresh gas: a new index of the efficiency of semi-closed breathing systems 474
P. C. W. Beatty, G. Meakin and T. E. J. Healy

Hepatic disposition of methohexitone in patients undergoing coronary bypass surgery 478
H. Lange, H. Stephan, C. Brand, S. Zielmann and H. Sonntag

Anaesthesia for critically ill children during magnetic resonance imaging 482
J. R. Tobin, E. A. Spurrier and R. C. Wetzel

Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat.. 487
J. A. Micol and M. L. Laorden

Enhancement of bupivacaine toxicity by diltiazem in anaesthetized dogs 492
B. A. Finegan, R. W. Whiting, Y. K. Tam and A. S. Clanachan

REVIEW ARTICLE

Perioperative blood loss and its reduction: the role of the anaesthestist 498
P. Simpson

SHORT COMMUNICATIONS

In vitro displacement of vasoactive mediators from plasma proteins: a possible mechanism for pseudo-allergic reactions to neuromuscular blocking drugs .. 508
W. R. Williams and D. J. Shale

Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia 511
M. Mayer, A. Doenicke, A. Hofmann and K. Peter

CASE REPORTS

Plasma lignocaine concentrations associated with extradural analgesia in patients with and without multiple organ failure 513
C. Putensen, W. Lingnau, G. Putensen-Himmer and M. Herold

Anaesthesia for Caesarean section in a patient with Ehlers–Danlos syndrome type IV 517
D. Brighouse and B. Guard

Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine 520
B. Tehan

APPARATUS

Bacterial retention properties of heat and moisture exchange filters 522
M. G. Lee, J. L. Ford, P. B. Hunt, D. S. Ireland and P. W. Swanson

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Leicester Meeting, July 10–11, 1992 .... 526P

CORRESPONDENCE

Retrograde intubation using the subcricoid region 542
Ventilatory effects of laparoscopy under general anaesthesia 542
European Standardization Committee on Anaesthetic Equipment 543
Radioimmunoassay tests and anaphylaxis 543
Respiratory depression after extradural fentanyl 544
A puncture technique for continuous subarachnoid block 544
Bacterial overgrowth and gastric dysfunction 545

BOOK REVIEWS

Emergency Medicine and the Anaesthetist 546
MCQ for Higher Examinations in Clinical Pharmacology 546
Clinical Practice of Regional Anesthesia 546
Maternal Mortality—The Way Forward. Some Implications of the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–87 547
Critical Care Toxicology 547
Manual of Obstetric Anesthesia, 2nd Edn 547

DECEMBER

EDITORIAL: The era of relaxant anaesthesia 551
J. E. Utting

ORIGINAL ARTICLES

Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia 554
T. H. Madej, R. G. Wheatley, I. J. B. Jackson and D. Hunter

Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia 558
R. G. Wheatley, D. Shepherd, I. J. B. Jackson, T. H. Madej and D. Hunter

Effects of isoflurane anaesthesia on the median nerve somatosensory evoked potential in children 562
D. G. Mason, D. Higgins, S. G. Boyd and A. R. Lloyd-Thomas

Sequential measurement of the median nerve somatosensory evoked potential during isoflurane anaesthesia in children 567
D. G. Mason, D. Higgins, S. G. Boyd and A. R. Lloyd-Thomas

Propofol and alfentanil in children: infusion technique and dose requirement for total i.v. anaesthesia 570
B. L. Browne, C. Prys-Roberts and A. R. Wolf

Pharmacokinetics of lignocaine in children after infiltration for cleft palate surgery 577
S. Michael, I. Barker, P. Henderson, R. W. Griffiths and C. S. Reilly

Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure 580
D. R. Cook, J. A. Freeman, A. A. Lai, Y. Kang, R. L. Stiller, S. Aggarwal, J. C. Harrelson, R. M. Welch and B. Samara

Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum 586
Z. Esener, B. Sarihasan, H. Güven and E. Üstün

Spinal anaesthesia for Caesarean section: comparison of 22-gauge and 25-gauge Whitacre needles with 26-gauge Quincke needles 589
L. E. Shutt, S. J. Valentine, M. Y. K. Wee, R. J. Page, A. Prosser and T. A. Thomas

Effect of fentanyl on ventilatory resistances during barbiturate general anaesthesia 595
R. Cohendy, J. Y. Lefrant, M. Laracine, T. Rebiere and J. J. Eledjam

Accuracy of coagulation studies performed on blood samples obtained from arterial cannulae 599
S. R. Haynes, W. Allardyce, B. Cowan and P. Tansey

Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery 602
K. D. Stühmeier, B. Mainzer, W. Sandmann and J. Tarnow

Evaluation of closed loop control of arterial pressure during hypotensive anaesthesia for local resection of intraocular melanoma 607
S. Chaudhri, J. R. Colvin, J. G. Todd and G. N. C. Kenny

Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs 611
D. Laroche, C. Lefrançois, J.-L. Gérard, F. Dubois, M.-C. Vergnaud, J.-L. Guéant and H. Bricard

Modulation by carbon dioxide and pH of the contractile responses to potassium and prostaglandin $F_{2\alpha}$ in human pial arteries 615
P. Reinstrup, T. Uski and K. Messeter

REVIEW ARTICLE

Massive blood transfusion 621
M. D. J. Donaldson, M. J. Seaman and G. R. Park

SHORT COMMUNICATIONS

Retrograde intubation—a facilitated approach 631
S. S. Dhara

Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour 634
S. McHale, V. Mitchell, S. Howsam and F. Carli

Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy 637
M. Welte, E. Haimerl, J. Groh, J. Briegel, L. Sunder-Plassmann, A. Herz, K. Peter and C. Stein

An active heat and moisture exchanger 640
F. Kapadia, M. P. Shelly, J. M. Anthony and G. R. Park

Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol 643
J. M. Murray and T. R. Trinick

CASE REPORTS

Apparent pacemaker failure caused by activation of ventricular threshold test by a magnetic instrument mat during general anaesthesia 645
J. P. Purday and R. M. Towey

Extradural abscess complicating extradural anaesthesia for Caesarean section 647
W. D. Ngan Kee, M. R. Jones, P. Thomas and R. J. Worth

General anaesthesia and the hypereosinophilic syndrome: severe postoperative complications in two patients 653
G. Samson, M. E. Wood, A. B. Knight-George and R. P. Britt

Use of suction catheters as an alternative to tracheal tubes in adults 657
P. S. Gataure, I. P. Latto and H. Taylor

COMMENTARY

Guest reviewers for 1992 659

CORRESPONDENCE

Hypoxaemia and insertion of the laryngeal mask airway 661
Vocal cord movement on induction of anaesthesia 661
Spinal anaesthesia for Caesarean section 662
Metallic fragments and the combined spinal-extradural technique 662
Inspiratory to end-tidal oxygen difference 663
Pre-emptive extradural analgesia 663
Skin injury with a pulse oximeter 665

BOOK REVIEWS

Respiratory Monitoring (*Contemporary Management in Critical Care* series) 666
Principles of Measurement and Monitoring in Anaesthesia and Intensive Care, 3rd Edn. 666
Anaesthesia for Ophthalmic and Otolaryngologic Surgery 667
Kinetics of Anaesthetic Drugs in Clinical Anaesthesiology 667
MCQ Companion to the Textbook of Anaesthesia 667
Plasma Volume Expansion 668

Index to Volume 69 669

SUPPLEMENT

Introduction 1S
D. J. Rowbotham and G. Smith

SYMPOSIUM ON POSTOPERATIVE NAUSEA AND VOMITING

Physiology of nausea and vomiting 2S
P. L. R. Andrews

The study of postoperative nausea and vomiting 20S
K. Korttila

Surgical and patient factors involved in postoperative nausea and vomiting 24S
J. Lerman

Postoperative nausea and vomiting in day-case surgery . 33S
B. V. Netchler

Anaesthetic factors contributing to postoperative nausea and vomiting 40S
P. G. Rabey and G. Smith

Current management of postoperative nausea and vomiting 46S
D. J. Rowbotham

The role of 5-HT in postoperative nausea and vomiting 60S
K. T. Bunce and M. B. Tyers

5-HT$_3$ antagonists in postoperative nausea and vomiting 63S
D. Russell and G. N. C. Kenny